

<b>Friedrich</b>	Heike	Germany	Improvement of Solubility and Stability of Poorly Soluble Drugs	2004
<b>Ciper</b>	Mesut	Turkey	Fast Disintegrating Solid Dosage Forms for the Oral Cavity	2004
<b>Lecomte</b>	Florence	France	pH-sensitive Polymer Blends used as Coating Materials in Controlled Drug Delivery Systems	2004
<b>Luan</b>	Xiasong	China	Biodegradable Microparticles and in situ forming Microparticles for Controlled Drug Delivery	2005
<b>Mohamad</b>	Ahmad	Syria	Oral Modified Drug Delivery Systems	2005
<b>Voigt</b>	Vivian	Columbia	Biodegradable Implants and in situ Forming Implant- and Microparticles- Systems	2005
<b>Dong</b>	Wenyu	China	Multiparticulate Drug Delivery System for Poorly Soluble Drugs and Macromolecule Drugs	2005

**CURRENT Ph.D. STUDENTS**

<b>Name</b>	<b>First Name</b>	<b>Country</b>	<b>Title -Dissertation</b>	<b>Jahr</b>
<b>Bley</b>	Oliver	Germany		
<b>Curbach</b>	Christine	Germany		
<b>Dickenhorst</b>	Burkhard	Germany		
<b>Möbus</b>	Katrin	Germany		
<b>Körber</b>	Martin	Germany		
<b>Mota</b>	Joana	Portugal		
<b>Raiwa</b>	Araya	Thailand		
<b>Rujvivipat</b>	Soravoot	Thailand		
<b>Schulz</b>	Martin	Germany		
<b>Shuwisitkul</b>	Duangrat	Thailand		
<b>Steiner</b>	Katrin	Germany		
<b>Sticha</b>	Dirk	Germany		
<b>Terebesi</b>	Ildikó	Germany		

**VISITING PROFESSOR/SCIENTISTS**

Year	Name	First Name	Country	Period
1997	Adhikari	Kaji Ram	Nepal	01.11.97 – 31.05.98
2000	Nada, Prof. Dr.	Aly	Egypt	07. - 09.2000
2001	Peppas, Prof. Dr.	Nicholas A.	U.S.A.	01. - 03.2001
2001	Sun	Huajun	China	04.11.-31.01.02
2001	Quan	Shancong	China	04.11.-31.01.02
2002	Zhu	Quangang	China	05.- 07.02
2002	Yang	Zhangwei	China	05.- 07.02

**POST DOCTORAL SCIENTISTS**

Year	Name	First Name	Country	Period
1997	Dashesky, Dr.	Andrei	Ukraine	01.11.97 -
2002	Hoffart, Dr.	Valerie	France	01.11.02 – 31.8.2005
2003	Skupin, Dr.	Marc	Germany	01.02.03 – 31.05.2004
2004	Pearnchob, Dr.	Nantharat	Thailand	01.04.04 – 31.01.2005
2004	Ciper, Dr.	Mesut	Turkey	01.05.04 -
2005	Dong, Dr.	Wenyu	China	01.02.05 -
2005	Charoenthai, Dr.	Nattawut	Thailand	01.09.05 -1.4.2006
2005	Ahmed, Dr.	Abid	Pakistan	01.07.05 -

**DAAD-STIPENDS**

Year	Name	First Name	Country	Period
1998	Im-Emsap	Wandee	Thailand	1998-2003
2001	Sungthongjeen	Srisagul	Thailand	01.06.-31.01.02
2001	Mohamad	Ahmad	Syrien	01.06.01 – 30.06.05
2002	Sathaporn	Nimkulrat	Thailand	01.12.02–31.05.03

**PRACTICAL STUDENTS**

Name	First Name	Country	Period
Körber	Martin	Germany	11.2000 – 07.2001
Herrmann	Ilka	Germany	11.2001 – 04.2002
Möschwitzer	Jan	Germany	01.2002 – 09.2002
Schneider	Annett	Germany	08.2002 – 01.2003
Streubel	H.-J.	Germany	03.2002 – 08.2002
Steiner	Katrin	Germany	05.2003 – 10.2003

**EXCHANGE STUDENTS**

<b>Year</b>	<b>Name</b>	<b>First Name</b>	<b>Country</b>	<b>Period</b>	<b>Sponsor</b>
1996	<b>Cordeiro Cardoso</b>	Juliana	Brasil	01.07.-31.10.96	
1997	<b>Gougeon</b>	Hugo	France	01.05.-31.07.97	ERASMUS/SOKR ATES
1998	<b>Adhikari</b>	Kaji Ram	Nepal		
1998	<b>Cerea</b>	Matteo	Italy	01.05.-31.07.98	ERASMUS/SOKR ATES
1998	<b>Lecomte</b>	Florence	France	01.05.-31.07.99	ERASMUS/SOKR ATES
1998	<b>Madeira</b>	Susana	Portugal		
1999	<b>Catharino</b>	Silvia	Brasil		
1999	<b>Lemorzadec</b>	Claire	France	01.05.-31.07.99	ERASMUS/SOKR ATES
1999	<b>Lopez Pereira</b>	César	Spain	01.03.-31.05.99	ERASMUS/SOKR ATES
1999	<b>Perini</b>	Luca	Italy	04.11.-07.02.00	ERASMUS/SOKR ATES
1999	<b>Tarenghi</b>	Anna	Italy		
2000	<b>Heinrichs</b>	Marie	France	03.07.-29.09.00	ERASMUS/SOKR ATES
2000	<b>Larbre</b>	Juliette	France	01.05.-31.07.00	ERASMUS/SOKR ATES
2001	<b>Garcia de la Barrera</b>	Mercedes	Spain	01.05.-17.07.01	ERASMUS/SOKR ATES
2001	<b>Le Brun</b>	Virginie	France	01.05.-31.07.01	ERASMUS/SOKR ATES
2001	<b>Mayer</b>	Véronique	France	16.09.-05.02.02	ERASMUS/SOKR ATES
2001	<b>Haun</b>	Youssef	Brazil	15.03.-30.06.01	
2001	<b>Viyoch</b>	Jarupa	Japan	01.04.-31.07.01	
2002	<b>Gaschard</b>	Diane	France	01.05.-31.07.02	ERASMUS/SOKR ATES
2002	<b>Martinez Alvarez</b>	Ana	Spain	15.05.-31.07.02	ERASMUS/SOKR ATES
2002	<b>Severino Das Neves</b>	Natericia	Portugal	15.05.-31.07.02	ERASMUS/SOKR ATES
2003	<b>Vandeveld</b>	Florence	France	01.05. - 01.08.03	ERASMUS/SOKR ATES
2003	<b>Jaraswekin</b>	Saowanee	Thailand	01.08. - 31.05.04	DAAD
2003	<b>Del Rio Medel</b>	Leticia	Portugal	09.10. - 22.12.03	ERASMUS/SOKR ATES
2004	<b>Burgos</b>	Ana	Spain	22.09. - 16.12.04	ERASMUS/SOKR ATES
2004	<b>Bottelo</b>	Giorgia	Italy	01.07. - 30.09.04	ERASMUS/SOKR ATES

2004	<b>Betrand</b>	Coralie	France	01.05. – 31.07.04	ERASMUS/SOKR ATES
2004	<b>Mota</b>	Joana	Portugal	05.04. – 13.07.04	ERASMUS/SOKR ATES
2004	<b>Panos Perez</b>	Ines	Spain	01.10. – 31.12.04	Programa Nacional de Formación de Profesorado Universitario
2005	<b>Menard</b>	Timothé	France	01.06. – 31.08.05	ERASMUS/SOKR ATES

# EXHIBIT 26

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE

**BIOVAIL LABORATORIES  
INTERNATIONAL SRL**  
a corporation of Barbados,

Plaintiff,

Y.

ANDRX PHARMACEUTICALS, LLC  
and ANDRX CORPORATION

Defendants.

C.A. No. 05-586-GMS

C.A. No. 05-730-GMS

C.A. No. 06-620-GMS

CONSOLIDATED

REDACTED -

PUBLIC VERSION

**DECLARATION OF SANFORD M. BOLTON, PH.D.  
IN SUPPORT OF ANDRX PHARMACEUTICALS, LLC'S  
and ANDRX CORPORATION'S CLAIM CONSTRUCTION**

OF COUNSEL:

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FOLEY & LARDNER, LLP  
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**Martin P. Endres**  
**HEDMAN & COSTIGAN, P.C.**  
1185 Avenue of the Americas  
New York, New York 10036  
Tel: (212) 302-8989

Dated: April 19, 2007  
784479 / 30015

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*Attorneys for Defendants Andrx  
Pharmaceuticals, LLC and Andrx  
Corporation*

I, Dr. Sanford M. Bolton, declare and state as follows:

**A. INTRODUCTION**

1. My name is Dr. Sanford M. Bolton. As detailed in my Curriculum Vitae, attached to this report as Exhibit A, after having been involved with various aspects of pharmaceutical sciences for more than 50 years, I am now a consultant to the pharmaceutical industry. I have special expertise in (1) biopharmaceutics and pharmacokinetics - the study of rates of absorption, distribution, metabolism and elimination of a drug substance and (2) biostatistics.

2. Andrx Pharmaceuticals, Inc. ("Andrx") has retained me as an expert in this case. My scientific, technical and specialized knowledge may assist the trier of fact to understand the evidence and/or to determine the facts at issue in this case relating to an understanding of the statistical terminology used in United States Patent No. 7,108,866 ("the '866 patent") (a copy of the '866 patent is attached hereto as Exhibit B).

**I. QUALIFICATIONS AND BACKGROUND**

**A. QUALIFICATIONS**

3. I am qualified as an expert because of my knowledge, skill, experience and training in some of the areas at issue in this litigation. My education and professional qualifications to testify in this case are described below.

**1. Areas of Expertise**

4. My primary areas of expertise relevant to this case are in the areas of bioavailability assessment and biostatistics. Bioavailability is the study of the rate and amount of drug that reaches the general circulation from an administered dosage form. Biostatistics is the

statistical study of biological investigations and may be divided into four parts: (1) the design of the experiment, (2) collection of data, (3) analysis of the data collected and (4) interpretation of the analysis.

## 2. Education

5. I have a Ph.D. in Pharmacy with a minor in physical chemistry from the University of Wisconsin. My thesis concerned tetracycline interactions and was entitled, "Complexation of Tetracycline with Organic Molecules."

6. I have two Masters degrees - a Masters in Pharmaceutics from the University of Wisconsin and a Masters in Biostatistics from Columbia University.

7. I received a Bachelor of Pharmacy degree from Rutgers University in New Jersey.

## 3. Professional History

8. I have been involved with various aspects of the pharmaceutical field for more than 50 years. I have worked as a retail pharmacist (previously registered in New York and New Jersey), as a teacher and researcher, as Director of Statistics, as Director of Quality Control, and as Director of Research Coordination in the pharmaceutical industry. Prior to retiring, I was professor and chairman of the Pharmacy Department at St. John's University where I mentored many graduate students and taught biostatistics and biopharmaceutics/pharmacokinetics. In all, I have spent over twenty years in academia during which I have taught biostatistics, biopharmaceutics and pharmacokinetics, physical pharmacy and pharmaceutics. Many of my graduate students are now or have been engaged in pharmaceutical research, administration and academia, and include several corporate vice presidents, a Dean of a College of Pharmacy, a Director at the Food and Drug Administration ("FDA") and a C.E.O. of a pharmaceutical company.



9. I have performed work as a statistician for 40 years. I have considerable experience with pharmaceutical and related statistical problems of a very varied nature. In particular, I have been closely involved with bioavailability/bioequivalence studies from a design and analysis viewpoint. I was a member of the FDA expert panel on Individual Bioequivalence. I have also set up and monitored clinical and bioequivalence studies as Associate Director of Medical Affairs for a pharmaceutical company. My experience includes analysis of quality control data and implementation of quality control data collection. Additionally, as a pharmaceutical scientist, I have had considerable experience in supervising and optimizing formulation of pharmaceutical dosage forms.

10. My career in the private pharmaceutical industry spans more than 14 years. After receiving my Masters in Biostatistics in 1966, I became the Director of Quality Control for Endo Laboratories. In 1970, I was recruited by Lever Brothers Research for the position of Senior Scientist, Head of Statistics. In 1975, I became the Director of Statistics and Clinical Research Coordination at USV Laboratories. Currently, I serve as a consultant to the pharmaceutical industry including major pharmaceutical companies.

#### 4. Publications, Presentations, Honors and Public Service

11. I have authored more than 100 publications on the pharmaceutical sciences and biostatistics, including textbooks, chapters, and encyclopedias in use by pharmaceutical scientists worldwide. Notably, I have authored a text pertaining to biostatistics, "*Pharmaceutical Statistics*," of which the 4<sup>th</sup> edition recently has been published. Since 1990, I have authored the chapter on "Statistics" in each edition of *Remington's Pharmaceutical Sciences*. I have also published many papers on the topic including, *Flawed Statistical Analysis and Representation of Fact*, Drug Development and Industrial Pharmacy 23, 851-856 (1997); *Independence and*

*Statistical Inference*, Journal of Clinical Pharmacology (1998); *When is it Appropriate to Average...and the Barr Decision?*, Clinical Research and Regulatory Affairs (1994).

12. I hold several patents on pharmaceutical controlled release formulations. Representative publications in the area of dissolution and bioavailability include, *Optimization of Process Variables for the Preparation of Ibuprofen Coprecipitates with Eudragit S100*, International Journal of Pharmaceutics, 1 (1993); *Controlled Release Coprecipitates: Formulation Considerations*, Journal of Controlled Release (1996); *Outlier Tests and Chemical Assays*, Clinical Research and Regulatory Affairs 10, 159-175 (1993); *Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies*, Journal of the Association of Analytical Chemists, 75, 19A (1992).

13. I have also served on the Editorial Board of the *Journal of Clinical Research Practice and Drug Regulatory Affairs*. I am a reviewer for the *Journal of Pharmaceutical Sciences*, the *Journal of Pharmaceutical and Biomedical Analysis* and *Pharmaceutical Research*.

14. I have done substantial original research in the fields of my expertise. I have competed for and been awarded over \$300,000 in research grants and worked as the principal or co-principal investigator for this research. Many of these studies were on pharmaceutical formulations.

15. I have been invited to give presentations all over the world, for both private organizations and drug regulatory bodies including the *Food and Drug Administration/American Association of Pharmaceutical Scientists Meeting - Assay Validation in Bioavailability-Pharmacokinetic Studies - Quality Control, Statistical Considerations*, Washington, DC (1990); *Outliers in Bioequivalence Testing*, Drug Information Association Meeting, Bethesda, MD

(1991); *FDA Generic Expert Advisory Panel Meeting-Individual Bioequivalency*, Silver Spring, MD (1993); *Individual Bioequivalence*, Conference on ANDAs, San Diego, CA (1998); *Formulation Optimization*, Aradigm, Hayward, CA (2000).

16. I have received a number of academic and professional honors. I am proud to have been the recipient of NIH grants and, at Columbia University, I had a NIH post-doctorate fellowship in statistics. I received the Gustavus Pfeiffer Award from the American Foundation For Pharmaceutical Education. I am a Fellow of the American Association of Pharmaceutical Scientists (AAPS).

**5. Retention in Other Matters**

17. In the past four years, I have given testimony either at trial or at a deposition as an expert in the following cases:

*Purdue Pharma. v. Endo Pharms., Inc.*, Case Nos. 00-8029, 00-2109, 01-8177 (S.D.N.Y.)

*GlaxoWellcome, Inc. v. Andrx Pharms., Inc.*, Case No. 99-7179 (S.D. Fla.)

*Eli Lilly v. Teva Pharmaceuticals* (S.D. Ind.) (concerning Sarafem)

*Johnson v. Ethicon, Inc.*, Case No. 01-1530 (Cir. Ct. Kanawha Cty. W. Va.)

*Solvay Pharms. v. KV Pharms.*, Case No. 03-2836 (D. Minn); and

*Abbott Labs. v. Andrx Pharmaceuticals, Inc.* Case No. 05 C 1490 (N.D. Ill.)

**6. Retention in This Case**

18. Andrx has retained me in this case to examine the '866 patent and related pharmacokinetic data.

19. I am being compensated at the rate of \$400 per hour for work and analysis and \$800 per hour for testimony. My compensation does not depend either on the conclusions I reach or the outcome of this case.

## **II. INFORMATION CONSIDERED IN THE PREPARATION OF THIS DECLARATION**

21. In preparing this declaration, I have relied on my over fifty years of professional and scientific experience as a researcher and scientist to evaluate the pharmacokinetic data presented to me. I also have relied on the types of facts or data that reasonably are relied on by experts in my fields of expertise in forming my opinions and inferences about the topics.

22. In connection with the opinions that I provide in this Declaration, I have reviewed the '866 patent, and two studies conducted by Biovail. The first study was Study #2293 (B99-428PK-DILG99) A Three-Way Single-Dose Open-Label Fasting and Fed Comparative Bioavailability Study of Diltiazem Hydrochloride Extended-Release (Tiazac® XL) Capsules (420 mg) Under Two Study Conditions (Morning, Evening Administration) in Normal Healthy Non-Smoking Male and Female Volunteers (BLS 053097-053831) (hereinafter Study #2293). The second study was Study # 2464 (B01-531PK-DILG 99) A Two-Way, Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability Study Between Diltiazem HCl Extended Release Bead Tablets (360 mg) with Evening Drug Administration (10:00 P.M.) and Diltiazem HCl Extended Release Bead Tablets (360 mg) With Morning (08:00 A.M.) Drug Administration in Normal Healthy Non-Smoking Male and Female Subjects (BLS 020384-020684) (hereinafter Study #2464).

23. Figure 9A and 9B of the '866 patent contain data for AUC and C<sub>max</sub> from a three way crossover for 29 subjects. The three treatments are "Morning Fasting", "Morning Fed" and "Night Dosing." I have analyzed this data based on only what is presented in the '866 patent and

using well-known statistical procedures for data presented in this manner. I then computed 90% confidence intervals for the ratio of the relevant parameters as described by the United States Food and Drug Administration for evaluating bioequivalence studies. Specifically, I performed a Two-Way Analysis of Variance comparing AUC and  $C_{max}$  with factors "Subjects" and "Treatments." The comparisons were performed for Morning Fed/Fast and Night/Morning Dosing. These factors were selected because they were the factors contained in the '866 patent. The results are shown in Table 1, based on a logarithmic transformation.

Table 1 Analysis of Patent Figures 9A and 9B  
Geometric Means

	Morning Fasted	Morning Fed	Night Dosing	Fed/Fasted (ratio)	Fed/Fasted 90% Confidence Interval	Night/Morning (ratio)	Night/Morning 90% Confidence Interval
AUC	3292.8	3671.2	3818.3	1.11	1.03-1.20	1.16	1.07-1.252
$C_{max}$	167.47	205.99	226.89	1.23	1.12-1.35	1.35	1.23-1.49

24. The FDA definition of bioequivalence regarding the ratio of parameters is a confidence interval that lies between 0.80 and 1.25 for the logarithmic transformed parameters (80-125%). Applying the FDA definition to the data in Figures 9A and 9B of the '866 patent, the product would not be considered bioequivalent when administered in the evening and in the morning because both the AUC and  $C_{max}$  value are outside the 0.80-1.25 confidence interval. In addition, the product would not be considered bioequivalent when administered in the morning under fed and fasted conditions because the  $C_{max}$  value is outside the 0.80-1.25 confidence interval.

25. The data in Figures 9A and 9B of the '866 patent appears to be taken from Study #2293 mentioned above, which was a single dose, three-way crossover study with 30 subjects. The '866 patent data had 29 subjects, and appears to omit data from subject #35 of Study #2293. I believe that the data in Figures 9A and 9B of the '866 patent were obtained from Study #2293 based upon a review of the data on page 078 of study #2293 (BLS053202) and the data of Figures 9A and 9B of the '866 patent. While in many instances the data were not identical, they were always very close. The averages for AUC for the three treatments using only the 29 subjects reported in the '866 patent are 3543.51, 3910.08 and 4082.48 for the Morning Fasted, Morning Fed and Night Dosing, respectively. The averages from the patent are 3542.88, 3910.4 and 4078.57 for the Morning Fasted, Morning Fed and Night Dosing, respectively. The statistical analysis reported in Study #2293 included other variables, Sequence, Period, Gender and Interaction, in addition to the Treatments and Subjects used in the Patent data analysis. The conclusions in Study #2293, using 30 subjects and all the above variables is that the AUC for the Night/Morning and Morning Fed/Fasted administrations are bioequivalent but that the  $C_{max}$  averages for the administrations showed a lack of bioequivalence. The relevant confidence intervals from the Biovail Study are shown in Table 2.

Table 2. Analysis of Biovail Data (BLS053122)

	AUC Ratio	90% Confidence Interval
Fed/Fasted (BLS053206)	1.120	1.05-1.20
Night/Morning (BLS053207)	1.156	1.08-1.236

	C <sub>max</sub> Ratio	90% Confidence Interval
Fed/Fasted (BLS053218)	1.235	1.13-1.35
Night/Morning (BLS053219)	1.355	1.24-1.48

26. Based on the above analyses and by analyzing the data in the '866 patent at face value, with no other information, it is my opinion that C<sub>max</sub> for Morning Fed/Fasted and Night/Morning are not bioequivalent. The analysis for AUC for Night/Morning shows lack of equivalence because the upper confidence interval is 1.252 which exceeds the FDA upper limit of 1.25. The analysis for AUC for Morning Fed/Fasted shows bioequivalence.


27. The analysis of data from Study #2293 shows equivalence for AUC comparisons, and lack of equivalence for C<sub>max</sub> comparisons for Fed/Fasted and Night/Morning. These analyses used 30 subjects compared to 29 subjects reported in the '866 patent, and included variables in the analysis not identified in the '866 patent.

28. I have also reviewed Study # 2464. I have been informed by counsel for Andrx that portions of this study were provided to the United States Patent and Trademark Office during prosecution of the '866 patent. **REDACTED**

REDACTED

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge.

April 20, 2007  
Dated

  
Sanford M. Bolton, Ph.D



**TAB A**

CURRICULUM VITAE

Sanford M. Bolton, PH.D.  
67 Phelps Avenue, Cresskill, NJ 07626  
5495 N.Via Velazquez, Tucson, AZ 85750

CURRENT POSITION

Consultant

EDUCATION

B.S.	1952	Rutgers University	Pharmacy
M.S.	1956	U. Wisconsin	Pharmacy
Ph.D.	1958	U. Wisconsin	Pharmacy
M.S.	1966	Columbia University	Biostatistics

PROFESSIONAL EXPERIENCE

2005-Present Lecturer on Statistics for course for Regulatory in  
Pharmaceutical Industry  
1980-Present Consultant to numerous generic and brand  
pharmaceutical companies  
1994-2007 Visiting Professor, U. Arizona, Tucson, AZ  
1993-1995 Adjunct Professor, St. John's U., New York  
1991-1994 Professor, Department PAS, St. John's University, New  
York  
1980-1991 Professor, Chairman, Department PAS,  
St. John's University, New York  
1975-1980 Director, Statistics and Clinical  
Research Coordination, U.S.V. Labs  
1970-1975 Senior Scientist, Head of statistics,  
Lever Brothers Research, New Jersey  
1968-1974 Adjunct Professor, Columbia College of Pharmacy  
  
1966-1970 Director, Quality Control, Endo  
Labs., Garden City, New York  
1958-1966 Associate Professor, University of Rhode Island  
1952-1954 Retail Pharmacist (Registered, NJ, NY)

COURSES TAUGHT

Biostatistics (Graduate)  
Biopharmaceutics and Pharmacokinetics  
Physical Pharmacy  
Pharmaceutics

GRADUATE STUDENTS

Advisor to 30 Ph.D. and 20 M.S. students. These students are now  
engaged in research, administration and academia, and include,  
several vice presidents, a Dean of a College of Pharmacy and C.E.O.  
of a major pharmaceutical company.

SOCIETIES

American Association of Pharmaceutical Scientists

OTHER

Fellow, American Association of Pharmaceutical Scientists (AAPS)

Editorial Board, Journal of Clinical Research Practice and Drug  
Regulatory Affairs

Reviewer for Journal of Pharmaceutical Sciences, J. pharm. and  
Biomed. Analysis, and Pharmaceutical Research.

Help with Recruitment at local level for AAPS.

FDA Expert Panel on Individual Bioequivalence

PUBLICATIONS

Complexes Formed in Solution by Homologs of Caffeine, Bolton and  
Higuchi, J. Am Pharm Assoc., Sci. Ed., 46, 38, 1957.

The Solubility and Complexing Properties of Oxytetracycline and  
Tetracycline III, Bolton and Higuchi, Ibid, 48, 557, 1959.

The Interaction of Citrate with Aspirin and Benzoic Acid, Ibid,  
Bolton, 49, 237, 1960.

A Note on the Stability of Aspirin in Solution, Drug Standards,  
Bolton, 28, 117, 1960.

Complexation of Organic Acides and Bases with their Salts in  
Aqueous Solution, Bolton and Valinotti, J. Pharm. Sci. 51,  
201, 1962.

Quantitative Study of Chelates of Pyridoxine-2-aldoxime, Bolton  
and Beckett, Ibid, 51, 533, 1962.

Chelatometric Determination of Ferrous Iron with 2-Pyridine  
Aldoxime as an Indicator, Ibid, Bolton, 52, 858, 1963.

Interaction of Urea and Thiourea with Benzoic and Salicylic  
Acids, Ibid, Bolton, 52, 1071, 1963.

PUBLICATIONS (continued)

- Book Review, Am. J. Pharm. Ed., 28, 622, 1964.
- Metal Chelates as Potential Reactivators of Organic Phosphate Poisoned Acetylcholinesterase, Bolton, J. Pharm. Sci., 53, 55, 1964.
- Investigation of 1, 3-Diaminopropanol-2 Interactions with Copper and Nickel Ions, Mario and Bolton, Anal. Chem., 37, 165, 1965.
- Inhibition of Acetylcholinesterase by Chelates I, J. Pharm. Sci., Bolton, 54, 373, 1965.
- Molindone, Fred. Proc. Abstracts, March - April 1967. 51 Anniversary meeting, 2685, Chicago, Illinois.
- Interaction of Aspirin with Urea in Water, J. Pharm. and Pharmacology, Bolton, 19, 550, 1967.
- Inhibition of Acetylcholinesterase by Chelates III, Mario and Bolton, J. Pharm. Sci., m 57, 418, 1968.
- Human Urinary Excretion of the Quarternary Ammonium Compounds Anisotropine Methylbromide and Propantheline Bromide, Bolton, et.al., Ibid, 57, 1375, 1968.
- Lab. Manual for Pharmaceutical Preps., with G. Osborne, Univ. of Utah Press, 1959.
- Circadian Variation of the Plasma 17-Hydroxy Corticosteroids in CNS Disease, Krieger and Krieger, J. Clin. Endocrinol. Metab., 26, 1929 (1966).
- Calculations of Release Rates from Sustained-Release Dosage Forms using the Wiley Method, J. Pharm, Sci., Bolton, 58. 1287. 1969.
- Correlation of Dental Calculus Weights with Volpe Manhold Index Scores, J. Peridontol, Bolton, et.al., 44, 535, 1973.
- A new Method for Assessing Inhibition of Gingivitis by Potential Therapeutic Agents, Bolton, et.al., Ibid, 44, 535, 1973.
- Dose Response of Chlorhexidine Gluconate in a Model in Vivo Plaque System, J. Dental Research, Bolton, et. al., 53, 94, 1974.

PUBLICATIONS (continued)

- Influence of Chlorhexidine and a Zinc Mouth Rise on Gingivitis, Bolton, et. al., IADR Abstract, 1974, J. Dent. Res., 53, 94, 1974.
- Antiplaque Effectiveness of Chlorhexidine Gluconate Under Different Toothbrushing Regimens, IADR Abstracts, J. Dental Research, Bolton, et. al., 53, 145, 1974.
- An End Point Clinical Technique for Assessing Inhibition of Gingivitis, Bolton, et. al., IADR Abstracts, J. Dental Research, 51, 201, 1972.
- Clinical Evaluation of a Newly Designed Contoured Toothbrush, J. Periodontol., Bolton, et. al., 47, 87, 1976.
- Dose Response to Chlorthalidone in Patients with Mild Hypertension, Clinical Pharm. Ther., Bolton, et. al., 24, No. 2, pp. 192-198, August, 1978
- Bioavailability and Pharmacokinetics of Chlorthalidone in Humans, Proceedings of Special Investigators Symposium, Bolton, et. al., White Plains, New York, Sept., 1978, MTP Press Ltd., 1979.
- Chlorthalidone 25 mg. -Highlights of the Statistical Analysis, Bolton, Ibid, 1979.
- The Pharmacist as a Drug Research Monitor, Sceusa, N., Vukovich, R.A., Sanford Bolton, Matoren, G. and Neiss, E.S., American Pharmacy, NS21, No. 4, April, 1981, pp. 44-46.
- Caffeine: Its Effects, Uses and Abuses, Sanford Bolton and Pressman, A.H., The Journal of Applied Nutrition, 33, No. 1, 1981, pp. 35-53.
- Caffeine - Psychological Effects, Use and Abuse, Sanford Bolton et. al., Journal of Orthomolecular Psychiatry, 210, No. 3, 1981, pp. 202-211.
- Laxatives - Use and Abuse, Physician East, November, 1981, Bolton, et. al., p. 20 and 23.
- Efficacy of Buccal Synchron Nitroglycerin in Patients with Angina Pectoris, Lichstein, E., Greengart, G., Sanford Bolton, Hollander, S. and Sanders, M., Advances in Pharmacotherapy, Vol. 1, 1982, pp. 166-173.

PUBLICATIONS (continued)

Methemoglobin Levels Produced by Commonly Used Nitrates, Asura, E., Guadanino, V., Lichstein, E., Sanford Bolton, Sanders, M., Hollander, G., and Greengart, A., Clin. Res., 30:168A, 1982 (Abstract).

Efficacy of Sustained Release Buccal Nitroglycerin in Patients with Angina Pectoris: New and Long Acting Therapy Demonstrated by Exercise, Greengart, A., Lichstein, E., Hollander, G., Sanders, M., Sanford Bolton, Clin. Res. 30:190A, 1982 (Abstract).

Predictive Value of Two Random 3 minute Ventricular Premature Beat Determinations, Lichstein, E., Jonas, S., Sanford Bolton, Hollander, G., Sanders, M. and Greengart, A., Clin. Res. 30:201A, 1982 (Abstract).

The Medical Uses of Garlic - Fact and Fiction, American Pharmacy, Bolton, et. al., NS22, No. 8, 40-43, August, 1982.

Angina Prophylaxis with Buccal Sustachron Nitroglycerin: A Rapid Onset, Long-Acting Nitrate, Reichek, N., Priest, C., Kienzle, M., Kleaveland, J.P., Bolton, Sanford, St. John Sutton, M., Advances in Pharmacotherapy, Vol. 1, 1982, pp. 143-154.

Clinical Significance of Slow Paroxysmal Atrial Tachycardia, Shani, J., Lichstein, E., Jonas, S., Greengart, A., Hollander, G., Sanders, M., and Sanford Bolton, Am. Heart J., 106, 478-483 (1983).

Efficacy of Sustained Release Buccal Nitroglycerin in Patients with Angina Pectoris: New and Long Acting Therapy Demonstrated by Exercise, Greengart, A., Lichstein, E., Hollander, G., Sanford Bolton, and Saunders, M., Chest, 83, 473-479 (1983).

Computation of In-House Quality Control Limits for Pharmaceutical Dosage Forms Based on Product Variability, S. Bolton, J. Pharm. Sci., 72, 405, 1983.

Factorial Designs in Pharmaceutical Stability Studies, S. Bolton, Ibid, p. 362.

Determination of Stability of Release Rates for Sustained Release Dosage Forms, Bolton, S., Proc. Pharm. Tech. Conf., Sept., 1982.

PUBLICATIONS (continued)

- Multicenter Dose-Response Study of Indapamide in the Treatment of Patients with Mild to Moderate Hypertension, Capone, P., Gollapudi, M., and Reeves, R.L., Clinical Therapeutics, 5, 305, 1983.
- The Use of Buccal Nitroglycerin in Patients with Angina Pectoris, Exercise Testing and Clinical evaluation, Lichstein, E., Greengart, A., Bolton, S., et al, Royal Society of Medicine, Concepts in Nitrate Delivery Systems, International Congress and Symposium, Series No. 54, 1982, p.99.
- Comparison of Time of Onset of Hemodynamic Effects of Sustained Release Buccal Nitroglycerin and Sublingual Nitroglycerin, Ibid, p. 143, Reichek, N., Priest, C., Bolton, S. et al.
- Book Review, Good Manufacturing Practices, J. Pharm. Sci., 72, 842, 1983.
- Chapter on "Statistics for Pharmaceutical Scientists" in "The Theory and Practice of Industrial Pharmacy", Edited by Lachman, Lieberman and Kanig, Third Edition, Lea and Febiger, Phila, 1986.
- A Pilot Study of Some Physiological and Psychological Effects of Caffeine, Bolton, Null, J. Ortho. Psychiatry, 13, 34 (1984).
- Essentials of Bioavailability Studies, Chapter in Concepts and Strategies in New Drug Development, Ed. Peter Nwanwu, Praeger, N.Y. (1983).
- Antianginal Efficacy of Sustained Release Buccal Isosorbide Dinitrate Tablets, Greengart, A., Lichstein, E., Hollander, G., Shani, J. and Bolton, S., Abstract, American Fed. Clin. Res., 1984.
- Evaluation of a new Fine Particulate Cellulose as a Direct Compression Tablet Aid, Parvez, R. and Bolton, S., Drug Development and Industrial Pharmacy, 11, 565-583 (1985).
- Process Validation for Hard Gelatin Capsules, S. Bolton, Drug and Cosmetic Industry, 42, August (1984).
- Area under Blood Level vs Time Curves at Steady State for Daily Doses at Unequal Dosing Intervals, S. Bolton, J. Pharm. Sci., 73, 150, (1984).

PUBLICATIONS (continued)

- Effect of Amino Acid Supplementation of Standard Rat Chow on Weight Gain of Weanling Rats, Bolton, S., Nicholazzi, F., Jarowski, C. and Trombetta, L., The J. of Applied Nutrition, 36, 172 (1984).
- Effect of Lysine, and Tryptophan Supplement on Normotensive and Hypertensive Rats treated with Chlorthalidone, Simonian, J., Bolton, S., Jarowski, C., Lynch, V., et. al., Ibid, 36. 27 (1984).
- Susadrin Transmucosal Tablets, Schor, J., Davis, S., Nigalaye, A. and Bolton, S., Drug Development and Industrial Pharmacy, 9, 1359 (1983).
- Manufacture of Crystalline Sorbitol Tablets - Effects of Mixing Time and Lubricants, Bolton, S. and Atluri, R., Drug and Cosmetic Industry, November (1984).
- Pharmaceutical Statistics: Practical and Clinical Applications, Bolton, S., Marcel Dekker, Inc., N.Y. (1984).
- Application of Factorial Designs in Kinetic Studies:  
Hydrolysis of Benzylpenicillin Solutions, Bolton, S., Reinstein, J., and Alobe, O., Int. J. Pharm. Tech. and Prod. Manufacture, 5, 6-12 (1984).
- Some Properties of the USP Content Uniformity Test, Bolton, S., J. Pharm. Sci. 74, 572 (1985).
- Basic Statistics for Clinical Monitors I, Bolton, S., Clin. Res. Pract. and Drug Reg. Affairs, 4, 19 (1986)
- Basic Statistics for Clinical Monitors II, Clin. Res. Pract. and Drug Reg. Affairs, Bolton, S., 5, (1), p. 61-80 (1987).
- US Patent: Sustained Release Therapeutic Compositions, 4,814,178, March 21, 1989.
- US Patent: Sustained Release Therapeutic Compositions, 4,814,179, March 21, 1989.
- Statistics for Clinical Monitors and Drug Regulatory Personnel, Bolton, S., Clinical Research Practices and Drug Regulatory Affairs, 7 (1), 1989.



PUBLICATIONS (continued)

- D. Saraiya and S. Bolton, The Use of Precirol to Prepare Sustained Release Tablets of Theophylline and Quinidine Gluconate, Drug Development Industrial Pharmacy, 16, 1963, 1990.
- In Vitro and In Vivo Release of Salicylic Acid from Povidone/Polydimethylsiloxane Matrices, R. Tarantino, D. Adair and S. Bolton, Drug Development Industrial Pharmacy, 16, 1217, 1990
- Investigation of Prolonged Drug Release form Matrix Formulations of Chitosan, A. Nigalaye, P. Adusumilli and S. Bolton, Drug Development Industrial Pharmacy, 16, 449, 1990.
- Stability of Morphine in Cormed III Intravenous Bags, American Journal of Hospital Pharmacy, L. Altman, S. Ahmed and S. Bolton, 47, 2040, 1990.
- The Influence of Tablet Buoyancy on the Human Oral Absorption of Sustained Release Acetaminophen Matrix Tablets, W. Phuapradit and S. Bolton, Drug Development Industrial Pharmacy, 1991.
- Drug Particle Size and Content Uniformity, S. Yalkowski, and S. Bolton, Pharmaceutical Research, 7, 962, 1990.
- Factorial Design in the Study of the Effects of Selected Liquid Chromatographic Conditions on Resolution and Capacity Factors, Ahmed, S. and Bolton, S., J. Liquid Chromatography, 13, 525-541, 1990.
- Remington's Pharmaceutical Sciences, Chapter "Statistics", 18th Ed, Mack, Phila, 1990.
- Pharmaceutical Statistics, Bolton, S., 650 pp., Second Edition, Marcel Dekker, NY, 1990.
- HPMC-Anionic Surfactant Interactions in Aqueous Systems, Alli, J., Bolton, S., Gaylord N., J. App. Polymer Science, 42, 947-956, 1991
- Synthesis, Characterization and In Vitro Evaluation of Polyvinyl Acetate Succinate vs Polyvinyl Acetate Phthalate as an Enteric Coating Polymer, Nached, H., Bolton, S. and Stephani, R., Submitted for publication, J. Pharm. Sci.

PUBLICATIONS (continued)

- Evaluation of New Hydrophilic Matrix Systems as Sustained Release Vehicles using a  $3^2$  Full Factorial Design, Adsumilli, P. and Bolton, S., Drug Development and Industrial Pharmacy, 17, 1931, 1991.
- Special Cubic Design in the Development of an Extended Release Tablet Formulation of a Highly Water Soluble Drug, Ahmed, S., Rahman, M. and Bolton, S., Submitted for publication, J. Pharm. Res.
- Lang, J.R. and Bolton, S., A Comprehensive Method Validation Strategy for Bioanalytical Applications in the Pharmaceutical Industry, Part I, J. Pharmaceutical Biomedical Analysis, 9(5), 357, 1991
- Lang, J.R. and Bolton, S., A Comprehensive Method Validation Strategy for Bioanalytical Applications in the Pharmaceutical Industry, Part II, J. Pharmaceutical Biomedical Analysis, 9(6) 1991
- Kislalioglu, S., Khan, M. and Bolton, S., Physical Characterization and Dissolution Properties of Ibuprophen-Eudragit Coprecipitates, J. Pharm. Sci., 80, 799, 1991
- W. Phuapradit and S. Bolton, The Influence of Tablet Buoyancy on the Human Oral Absorption of Sustained Release Acetaminophen Matrix Tablets, Drug Development Industrial Pharmacy, 1991.
- Vinod P. Shah, Bolton, S., et.al., Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies, Journal of AOAC, 75, 19A, 1992.
- Bolton, S., Should a single Unexplained Failing Assay be Reason to Reject a Batch?, Clin. Research and Reg. Affairs, 10(3), 159-175, 1993.
- Bolton, S., Outlier Tests and Chemical Assays, Clin. Research and Reg. Affairs, 10, 221-232, 1993.
- Degree of Complexation Between Partially Neutralized Polyacrylic Acid and Water-Soluble Cellulose Ethers I, A. Sheth, Gaylord, N. and Bolton, S., Submitted to J. App. Polymer Science

PUBLICATIONS (continued)

- When is it appropriate to average...and the Barr Decision?,  
Bolton, S., Clin. Research and Reg. Affairs, 1994
- Optimization of Process Variables for the Preparation of  
Ibuprofen Coprecipitates with Eudragit S100, Khan, MA,  
Bolton, S and Kislalioglu, MS, Int. J. Pharmaceutics, 1,  
1993.
- Remington's Pharmaceutical Sciences, Chapter "Statistics", 19th  
Ed, Mack, Phila., 1994
- Optimization of Iontophoretic Transdermal Delivery of a peptide  
and non-peptide drug, Gupta, S. Kumar, S, Bolton, S., Behl,  
C., Malick, A.W., J. Controlled Release, 30, 253-261, 1994
- Chapter on Statistics in Pharmacy for Encyclopedia of  
Pharmaceutical Technology, Volume 14, Swarbrick, J. and  
Boylan, J., Editor, Marcel Dekker, 1996
- Controlled Release Coprecipitates: Formulation Considerations,  
Khan, M.A., Bolton, S., et. al., J. Controlled Release, 1996
- HPLC Study of Binding of Sulfinpyrazone to Serum Albumin, Sun,  
C.F., Hsiao, C.L. and Bolton, S., Chromatographia, 42, 401,  
Apr., 1996
- Pharmaceutical Statistics, Bolton, 3rd Ed., Marcel  
Dekker, NY, NY, 1997
- Is it Necessary to Take small Blend Samples to Assess Drug  
Uniformity?, Bolton, S., Sharma, M., et. al, Pharm. Dev. and  
Technology, 2(3), 297-299, 1997.
- US Patent: Liquisolid Formulations, #5,800,834, Issued, 1998.
- Generic Warfarin: Implications for Patient Care-Another View,  
Meyer, M., Chan, K. and Bolton, S. Pharmacotherapy, 1998
- Flawed Statistical Analysis and Representation of Fact, Drug Dev.  
and Ind. Pharmacy, 23 (8), 851-856, 1997
- Independence and Statistical Inference, J. Clin. Pharmacology,  
1998
- US Patent: Liquisolid Formulations, #5,968,550, Issued, 2000.
- Clinical Study Design and Analysis, Bolton, S., Clin. Research  
and Reg. Affairs, p. 285, Vol 17, No. 4, 2000
- US Patent: Liquisolid Formulations, #6,096,337, Issued, 2001.

Pharmaceutical Statistics, Bolton, S. and Bon, C., Fourth Edition, Marcel Dekker, NY, November, 2004.

Remington's Pharmaceutical Sciences, Chapter "Statistics", 20th Ed, Mack, Phila, 2001

Interchangeability of Brand and Generic Clozapine, Submitted for Publication, Psychiatric Services, July, 2002

An Alternative Solution to the Distribution of the Individual Bioequivalence Metric, J. Drug Dev. and Ind. Pharmacy, 29, 4, 469-474, 2003.

Remington's Pharmaceutical Sciences, Chapter "Statistics", 21<sup>st</sup> Ed, Mack, Phila, In Process

Generic Thyroid, J. Pharm Res., AAPS, 2005

Chapter in Book on Generic Drug Development Process, Marcel Dekker, in Press, 2007

#### RECENT PRESENTATIONS

Development of an Optimal Formula with Molded Nitroglycerin Tablets Stabilized with Methylcellulose and Carboxymethylcellulose. Sanford Bolton and Aloha, O.T., Abstract published and Poster Presentation at 1982 Midwest Regional Meeting, American Pharmaceutical Association, Academy of Pharmaceutical Sciences. May 24, 1982.

Determination of Stability of Release Rates for Sustained Release Dosage Forms, Presentation at Pharm Tech Conference sponsored by "Pharmaceutical Technology," September, 1982

Bioavailability/Bioequivalence Studies, Sanford Bolton, Invited Speaker, Presentation at the American Federation for Clinical Research, Eastern Section, Meeting, October 3-6, 1982. Proceedings to be published - See under Publications).

Effects of Mixing Time and Lubricants on the Manufacture of Sorbitol Lozenges, Am. Pharmaceutical Association, New Orleans, April, 1983.

Process Validation of Hard Gelatin Capsules, Invited Speaker, NAPM Meeting, Rye, NY. Sept. 1983.

Sustained Release, Theory and Practice, Vick International, Invited Speaker, Egham, England and Paris, July, 1984.

Process Optimization, Vick International, Invited Speaker, Egham, England and Paris, July 1985.

Statistical Aspects of Process Validation, Pharmaceutical Sub-Group, Canadian Pharmaceutical Assoc., Invited Speaker, Toronto, Canada, October 15-16, 1985.

Goldman, R. and Bolton, S., Controlled Release Pellet Variability Problems in Mixtures, "11th Asian Congress", Bangkok, December 1986, (International organization), 5 pages.

S. Bolton, Should Bioavailability Parameters be Treated Equally? FDA Meeting on Bioavailability/Bioequivalence, Washington, D.C., November 1986, 10 pages.

J.R. Lang, W. Chern, R. DeMent and S. Bolton, A Statistical Approach to Bioanalytical Method Validation, AAPS 3rd Annual Meeting, Orlando, Florida, October 1988.

Practical Uses of Statistics, Invited Speaker, U. of Ky., College of Pharmacy, June, 1989.

Statistical Analysis of Bioavailability Data, Invited Speaker, Pfizer, Groton CT, April 1989.

Toronto Meeting on Bioavailability, Bio-International International Symposium, Invited Spaker, AAPS-FDA, Oct. 1989, Toronto, Canada. 1. Outliers in Bioavailability Studies. 2. Should Data be Normalized?

Massachusetts College of Pharmacy Annual Graduate symposium, Keynote Speaker, Optimization techniques, May, 1990.

AAPS-FDA Meeting, Washington D.C., December 3-5, 1990, Invited Speaker, Assay Validation in Bioavailability-Pharmacokinetic Studies- Quality Control, Statistical Considerations

Berlex Laboratories, Cedar Knolls, N.J., Invited Speaker, Statistical Applications in Pharmaceutical Research, December, 1990

Ciba-Geigy, Summit, N.J., Invited Speaker, Optimization in Pharmaceutical Research, December, 1990.

Discussion Leader, Fireside Chats, AAPS annual meeting, Washington, D.C., Nov. 17, 1991

Formulation Characteristics and Parameters of Powdered Solutions, Spireas, S.S., Bolton, S. and Savastano, L., AAPS annual meeting, Washington, D.C., Nov. 17, 1991

Rapid Release Powdered Solutions of Several Water-Insoluble Drugs, Spireas, S.S., Bolton, S., Lau-Cam, C. and Savastano, L., AAPS annual meeting, Washington, D.C., Nov. 17, 1991

Outliers in Bioequivalence Testing, Drug Information Association, National Organization, Aug. 3-5, 1991, Bethesda, Md., 10 pages.

Statistical Applications for Process Validation, Pharmaceutical Sciences Group, 3rd Annual Technical Conference, Oct 6-8, 1991, Toronto

American Association of Pharmaceutical Scientists, Annual Convention, Washington, D.C. November, 1991, Leader of Fireside Chat program on design of experiments.

Formulation Characteristics and Parameters of Powdered Solutions, Spireas, S.S., Bolton, S. and Savastano, L., AAPS annual meeting, Washington, D.C., Nov. 17, 1991

Rapid Release Powdered Solutions of Several Water-Insoluble Drugs, Spireas, S.S., Bolton, S., Lau-Cam, C. and Savastano, L., AAPS, Washington, D.C., Nov. 17, 1991

Invited Speaker, FDA Generic Expert Advisory Panel Meeting, Feb. 11, 1993, Silver Spring, Md., Individual Bioequivalency

Invited Speaker, PDA Tutorial, December 6, 1993, Bethesda, Md.

Invited Speaker, Statistical Issues in Pharmaceutical Research, Am. Assoc. of Pharm. Sci. annual meeting, San Diego, Nov, 1994

Invited Speaker, Short Course on Statistical Issues in Pharmaceutical Research, Am. Assoc. of Pharm. Sci. annual meeting, San Diego, Nov, 1994

Invited Speaker, NAPM Scientific Meeting, Rockville, MD, Bioequivalency Issues, October 1994.

Invited Speaker, SmithKline Beecham, Annual Meeting of QC Staff Philadelphia, PA, November 1994.

Invited Speaker, AAPS Annual Meeting, Miami, November 7, 1995, Individual Bioequivalence

Invited Speaker, AAPS Midwest Annual Meeting, Chicago, Statistical applications and Bioequivalence, May 24, 1996

Invited Speaker, McNeill Pharmaceuticals, Philadelphia, PA, June, 1996

Invited Speaker, Land O'Lakes Analytical Conference, University of Wisconsin, Land O'Lakes Wisconsin, July 23rd, 1996.

Invited Speaker, Abbott Labs., Chicago, Statistical applications in pharmacy and QC, February, 1997

Invited Speaker, AAPS Alza Corp., Palo Alto, CA,

Statistical applications and outliers in QC Testing, May 6, 1997

Invited Speaker, AAPS Annual Meeting, Boston,  
Individual Bioequivalence, November 5, 1997

Invited Speaker, Tutorial on Pharmaceutical Statistics, 50th  
Annual Deming Statistical Conference, Atlantic City, NJ,  
December 8, 1997

Invited Speaker, Short Course on Statistical Issues in  
Pharmaceutical Research, Am. Assoc. of Pharm. Sci. Washington,  
DC, 1998

Invited Speaker, Conference on ANDAs, San Diego,  
Individual Bioequivalence, November, 1998

Invited Speaker, Bioequivalence, Mutual Pharmaceutical,  
Bioequivalence, June, 1999

Invited Speaker, Barr Laboratories, Bioequivalence, March, 1999

Invited Speaker, Midwest Meeting of Pharma, Product Complaints  
and Adverse Events, Chicago, July, 1999.

Invited Speaker, Formulation Optimization, Aradigm, Hayward, CA  
September, 2000

Invited Speaker, Bioequivalence, Texas Tech. College of Pharmacy,  
Amarillo, Texas, March, 2002

Invited Speaker, Statistics for GLPs, ALA/AAPS, Boston, June,  
2004

Invited Speaker, Optimization, Watson Laboratories, June, 2005

Invited Speaker, Bioequivalence, Barr Labs, August, 2005

Invited Speaker, Statistics, USC College of Pharmacy, January,  
2006

#### RECENT ABSTRACTS AND POSTERS

Vincent Romeo, Sanford Bolton et al, Randomized Double-Blind  
Multiple Dose Study of the Antiemetic Effect of Intranasal  
(IN) Metochlopramide (M) Compared to Placebo for Cisplatin  
(CP) Induced Emesis, ASCO Meeting New Orleans, May 1988.

D. Saraiya and S. Bolton, The Use of Precirol in Sustained  
Release Quinidine and Theophylline Tablets, APhA National  
Meeting, Hawaii, 1987.



J.J. Shah, S. Bolton and A.W. Malick, Hydroxypropylcellulose: Evaluation of effects of Various Factors on Sustained Release Characteristics of Salicylic Acid from Compressed Tablets, APhA National Meeting, Hawaii, 1987.

R. Tarantino, D. Adair and S. Bolton, Controlled Drug Release from Polyvinyl-pyrrolidone (PVP)/Polydimethylsiloxane (PDMS) Matrices, Effect of PVP Molecular Weight, Concentration and Physical State on In-Vitro Release Rate of Salicylic Acid, AAPS 3rd Annual Meeting, Orlando, Florida 1988.

D.B. Ray and S. Bolton, In-Vitro Verification of Mathematical Model for Predicting the Mean Variance of Release Rates of a Mixture of Pseudoephedrine HCl Controlled Release Pellets with Different Release Characteristics, AAPS 3rd Annual Meeting, Orlando, Florida, October, 1988.

Ahmed, A., Lau-Cam, C., Bolton, S., Factorial Design in the Study of the Effects of Selected Chromatography Conditions on Resolution and Capacity Factors, AAPS Meeting, Atlanta Ga., Oct., 1989

Ahmed S., Bolton, S. and Trombetta, L., Formulation and In-Vitro and In Vivo Evaluation of a Sustained Release Tablet Dosage Form of a Highly Water Soluble Drug, AAPS Meeting, Atlanta Ga., Oct., 1989

Ahmed, S. and Bolton, S., Simplex Design in the Development of Sustained Release Tablet Formulations, AAPS Meeting, Atlanta Ga., Oct., 1989

Development of a Sustained Release Delivery System for Quinidine Gluconate using Glycerol Palmito Stearate, Saraiya, D. and Bolton, S., AAPS Annual Meeting, Las Vegas, November 1990.

Orthogonal Composite Design in the Development of an Extended Release Formulation of a Highly Water Soluble Drug. Ahmed, S., Rahman, M and Bolton, S., AAPS Annual Meeting, Las Vegas, November 1990.

Special Cubic Design in the Development of an Extended Release Tablet Formulation of a Highly Water Soluble Drug, Ahmed, S., Rahman, M. and Bolton, S., AAPS Annual Meeting, Las Vegas, November 1990.

Evaluation of New Hydrophilic Matrix Systems as Sustained Release Vehicles using a  $3^2$  Full Factorial Design, Adsumilli, P. and Bolton, S., AAPS Annual Meeting, Las Vegas, November 1990.

P & G Graduate Student Award, Effect of Polymer-Polymer Interactions in Carrier Bases on Controlled Release of Medicaments, Sheth, A., Gaylord, N. and Bolton, S., Graduate Symposium, AAPS Annual Meeting, Las Vegas, November 1990.



HPLC Assay of Enalaprilat for Quantitative Estimation in Iontophoretic Transdermal Delivery Studies, S.K. Gupta, S.Bolton, et. al., AAPS Annual Meeting, Washington, 1991.

Evaluation of Some Lipids as Excipients in Extreme Release Tablet Formulation. S. Ahmed and S. Bolton, AAPS Annual Meeting, Washington, 1991.

Formulation Optimization for Iontophoretic Transdermal Delivery of a Peptide and a Non-Peptide Drug, S.K. Gupta, S. Bolton, et. al., AAPS Annual Meeting, Washington, 1991.

A Novel Technique to Evaluate the Buccal Absorption of Drugs, R. Gambhir and S. Bolton, AAPS Annual Meeting, Washington, 1991.

Synthesis and Evaluation of Chitosan Citrate Complexes as Hydrophilic Matrices Using Full Factorial Designs, P.S. Adsumilli, S. Bolton, et. al., AAPS Annual Meeting, Washington, 1991.

Degree of Complexation Between Partially Neutralized Polyacrylic Acid and Water-Soluble Cellulose Ethers, A. Sheth, Gaylord, N. and Bolton, S., AAPS Annual Meeting, Washington, 1991.

Effect of Manufacturing Methods on the Release Profile of Pseudoephedrine HCl Using Precifac, Saraiya, D., Bolton, S. and Trombetta, L., AAPS Annual Meeting, Washington, 1991.

Process Optimization of Ibuprofen Coprecipitates with Eudragit S100, Khan, M., Bolton, S. and Kislalioglu, S., AAPS Annual Meeting, San Antonio, 1992.

Effect of Drug Loading, Chemical Enhancers and Conducting Gels on Cromolyn Sodium Iontophoretic Transdermal Delivery, Gupta, S. Bolton, S., et. al., AAPS Annual Meeting, San Antonio, 1992.

Theory and Practice of Liquisolid Compacts, S.Spireas, C.Lau-Cam, S.Bolton, AAPS Annual Meeting, Orlando, November, 1993

Bioequivalence of Nadolol, a case for  $C_{max}/AUC$ , Bolton, et.al., Abstract, AAPS annual meeting, San Diego, CA, Nov., 1994

The Effect of Assay variation of Sodium Warfarin Tablets on Steady State Plasma Warfarin Concentrations, AAPS annual meeting, Indianapolis, Indiana, November, 2000

The Interchangeability of Clozaril and Clozapine, Phoenix, AZ, May 28, 2001

GRANTS

Special Post-Doctoral Fellow - AAPE - Gustavus Pfeiffer Award, London, England, Chelsea Polytechnic College of Pharmacy, 1961-2

NIH Research Grant (1962 - 1966) Interaction of Chelates with Acetylcholine

NIH Special Post-Doctoral Fellow (1964 - 1966) Statistics

Vick Research Grant - Tablet Formulation - 1982

C.R. Bard, Inc., Evaluation of the Stability of Morphine Sulfate and Meperidine in Plastic Disposable Syringes, grant awarded, March 1986.

Beach Pharmaceuticals, Formulation Research on Liquid Dosage Forms of Thioridazine Hydrochloride Suspensions, grant awarded, October 1986.

Forest Laboratories, NY, Floating Tablet Technology, grants awarded, April, 1986-87, 1987-88.

New York State Science and Technology Foundation, Commercial Development of a Novel Sustained Release Floating Tablet Matrix, grant awarded, October 1987.

Nastech Pharmaceuticals, Hapauge, NY. Nasal Absorption of Drugs, grant awarded, October 1987.

Abel Health Management Services, Inc., Manhasset, NY, The Stabilities of Various Concentrations of Morphine Sulfate Solutions at two Temperatures in the Cormed III (Kalex) Ambulatory Infusion Bags, grant awarded April 1988.

Lachman Consultant Services, Inc., Westbury, NY, Preparation of Preliminary Tablet Formulations, grant awarded January 1988.

American Lecithin Company, Atlanta, GA, Tablets of Lecithin, March 1988.

Upjohn Company, Stability of Ampicillin, October 1987 - Present.

Glaxo Inc., Stability of Ranitidine Parenteral Solutions in Syringes, 1989.

Glaxo, Inc., Educational grant for book on Biopharmaceutics and Pharmacokinetics 1992.

Barr Laboratories, Evaluation of liqui-solid Compacts, January, 1997

# TAB B



US007108866B1

(12) **United States Patent**  
Albert et al.

(10) Patent No.: **US 7,108,866 B1**  
(45) Date of Patent: **Sep. 19, 2006**

(54) **CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF**

(75) Inventors: Kenneth Stephen Albert, Mt. Kisco, NY (US); Paul José Maes, Oakville (CA)

(73) Assignee: Biovalli Laboratories International SRL, St. Michael (BB)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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424/458; 424/465; 424/468; 424/469

(58) Field of Classification Search ..... 424/457,  
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See application file for complete search history.

#### (56) References Cited

#### U.S. PATENT DOCUMENTS

4,263,273 A 4/1981 Appelgren et al. .... 424/21

4,327,725 A 5/1982 Cortese et al. .... 128/260  
4,600,645 A 7/1986 Ghebre-Sellassie et al. 428/403  
4,612,008 A 9/1986 Wong et al. .... 604/892  
4,623,588 A 11/1986 Nuwayser et al. .... 428/402.24  
4,628,047 A 12/1986 Sakurai et al.

(Continued)

#### FOREIGN PATENT DOCUMENTS

EP 0 149 920 A2 12/1984

(Continued)

#### OTHER PUBLICATIONS

Klokkers-Bethke, K. et al., "Development of a multiple unit drug delivery system for positioned release in the gastrointestinal tract", *Journal of Controlled Release*, 15 (1991) 105-112.

(Continued)

Primary Examiner—S. Tran

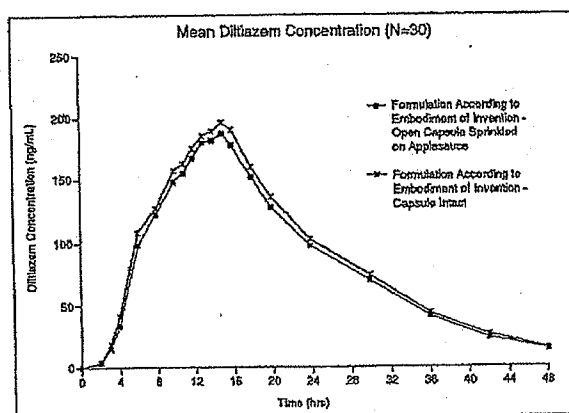
(74) Attorney, Agent, or Firm—Hunton & Williams; Robin L. Teskin

#### (57) ABSTRACT

A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a  $C_{max}$  of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and  
(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

88 Claims, 15 Drawing Sheets



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## U.S. PATENT DOCUMENTS

4,696,924 A	9/1987	Marcoux	514/211	5,622,716 A	4/1997	Barth	424/461
4,705,695 A	11/1987	Lehmann et al.	427/3	5,626,860 A	5/1997	Cincotta et al.	424/423
4,721,619 A	1/1988	Panoz et al.	424/459	5,654,005 A	8/1997	Chen et al.	424/480
4,753,802 A	6/1988	Stephens et al.	424/467	5,662,933 A	9/1997	Baichwal et al.	424/457
4,783,337 A	11/1988	Wong et al.	424/468	5,667,801 A	9/1997	Baichwal	424/457
4,784,858 A	11/1988	Ventouras	424/468	5,670,168 A	9/1997	Baichwal et al.	424/464
4,792,452 A	12/1988	Howard et al.	424/475	5,670,172 A	9/1997	Buxton et al.	424/495
4,808,413 A	2/1989	Joshi et al.	424/458	5,681,583 A	10/1997	Conte et al.	424/472
4,824,678 A	4/1989	Lindahl et al.	424/473	5,688,794 A	11/1997	Meier et al.	514/250
4,832,958 A	5/1989	Baudier et al.	424/473	5,716,933 A	2/1998	Meier et al.	514/12
4,839,177 A	6/1989	Colombo et al.	424/482	5,716,962 A	2/1998	Cincotta et al.	514/288
4,859,469 A	8/1989	Baudier et al.	424/462	5,736,159 A	4/1998	Chen et al.	424/480
4,859,470 A	8/1989	Guillard et al.	424/473	5,756,513 A	5/1998	Cincotta et al.	514/288
4,880,631 A	11/1989	Haslam et al.	424/424	5,773,025 A	6/1998	Baichwal	424/458
4,891,230 A	1/1990	Geoghegan et al.	424/461	5,785,994 A	7/1998	Wong et al.	424/473
4,894,240 A	1/1990	Geoghegan et al.	424/497	RE35,903 E	9/1998	Debregas et al.	424/458
4,917,899 A	4/1990	Geoghegan et al.	424/461	5,830,503 A	11/1998	Chen	424/480
4,938,967 A	7/1990	Newton et al.	424/458	5,834,023 A	11/1998	Chen	424/497
4,940,588 A	7/1990	Sparks et al.	424/490	5,834,024 A	11/1998	Heinicke et al.	424/497
4,952,402 A	8/1990	Sparks et al.	424/419	5,837,379 A	11/1998	Chen et al.	424/465
4,960,596 A	10/1990	Debregas et al.	424/458	5,840,329 A	11/1998	Bai	424/458
4,966,769 A	10/1990	Guillard et al.	424/473	5,843,347 A	12/1998	Nguyen et al.	264/9
5,000,962 A	3/1991	Sangekar et al.	424/482	5,846,563 A	12/1998	Baichwal	424/457
5,002,776 A	3/1991	Geoghegan et al.	424/497	5,851,555 A	12/1998	Sanghvi et al.	424/464
5,004,614 A	4/1991	Staniforth	424/466	5,869,097 A	2/1999	Wong et al.	424/473
5,008,114 A	4/1991	Lovrecich	424/484	5,914,134 A	6/1999	Sharma	424/497
5,051,262 A	9/1991	Panoz et al.	424/468	5,916,595 A	6/1999	Chen et al.	424/480
5,055,306 A *	10/1991	Barry et al.	424/482	5,922,352 A	7/1999	Chen et al.	424/465
5,082,668 A	1/1992	Wong et al.	424/473	5,945,125 A	8/1999	Kim	424/473
5,112,621 A	5/1992	Stevens et al.	424/497	5,958,456 A	9/1999	Baichwal et al.	424/489
5,149,542 A	9/1992	Valducci	424/493	6,004,582 A	12/1999	Faour et al.	424/473
5,156,850 A	10/1992	Wong et al.	424/473	6,022,562 A	2/2000	Autant et al.	424/489
5,160,744 A	11/1992	Jao et al.	424/473	6,033,687 A	3/2000	Heinicke et al.	424/497
5,175,003 A	12/1992	Goldman	424/484				
5,178,867 A	1/1993	Guillard et al.	424/473				
5,190,765 A	3/1993	Jao et al.	424/473				
5,219,621 A	6/1993	Geoghegan et al.	424/462				
5,229,135 A	7/1993	Philippon et al.	424/494				
5,252,338 A	10/1993	Jao et al.	424/473				
5,260,068 A	11/1993	Chen	424/451				
5,260,069 A	11/1993	Chen	424/451				
5,275,824 A	1/1994	Carli et al.	424/490				
5,286,497 A *	2/1994	Hendrickson et al.	424/490				
5,288,505 A	2/1994	Deboeck et al.	424/497				
5,326,571 A	7/1994	Wright et al.	424/473				
5,330,761 A	7/1994	Baichwal	424/469				
5,336,504 A	8/1994	Geoghegan et al.	424/462				
5,344,657 A	9/1994	Desmolins	424/458				
5,354,556 A	10/1994	Sparks et al.	424/419				
5,364,620 A	11/1994	Geoghegan et al.	424/497				
5,419,917 A	5/1995	Chen et al.	429/469				
5,439,689 A	8/1995	Hendrickson et al.	424/490				
5,445,829 A	8/1995	Paradissis et al.	424/480				
5,449,521 A	9/1995	Lovrecich	424/489				
5,455,046 A	10/1995	Baichwal	424/457				
5,458,887 A	10/1995	Chen et al.	424/464				
5,458,888 A	10/1995	Chen	424/464				
5,464,633 A	11/1995	Conte et al.	424/480				
5,470,584 A	11/1995	Hendrickson et al.	424/490				
5,472,708 A	12/1995	Chen	424/451				
5,472,711 A	12/1995	Baichwal	424/468				
5,478,574 A	12/1995	Baichwal et al.	424/485				
5,508,040 A	4/1996	Chen	424/451				
5,512,297 A	4/1996	Baichwal	424/451				
5,529,790 A	6/1996	Bichel et al.	424/480				
5,529,791 A	6/1996	Deboeck et al.	424/494				
5,554,387 A	9/1996	Baichwal	424/488				
5,558,879 A	9/1996	Chen et al.	424/480				
5,567,441 A	10/1996	Chen	424/494				
5,601,845 A	2/1997	Buxton et al.	424/495				
5,616,345 A	4/1997	Geoghegan et al.	424/497				

## FOREIGN PATENT DOCUMENTS

EP	0 263 083 A1	9/1987
EP	0 282 698 A	1/1988
EP	0 309 051 A1	9/1988
EP	0 320 097 A1	10/1988
EP	0 856 313 A1	10/1988
EP	0 315 414 A1	11/1988
EP	0 318 398 A1	11/1988
EP	0 322 277 A1	12/1988
EP	0 340 105 A1	4/1989
EP	0 342 106 A1	5/1989
EP	0 373 417 A1	11/1989
EP	0 605 174 A	12/1993
EP	0 527 637 B1	4/1998
EP	0856313 *	8/1998
EP	0 682 945 B1	6/1999
EP	0 591 424 B1	9/1999
WO	WO 90/06107	6/1990
WO	WO 91/01722	2/1991
WO	WO 93/0093	1/1993
WO	WO 93/0093 A1 *	1/1993
WO	WO 93/09767	5/1993
WO	WO 96/29992	10/1996
WO	WO 97/23219	7/1997
WO	WO 97/48386	12/1997
WO	WO 98/32424	7/1998
WO	WO 98/33488	8/1998
WO	WO 98/33489	8/1998

## OTHER PUBLICATIONS

Deedwanian, C. et al., Effect of Morning Versus Evening Dosing of Diltiazem on Myocardial Ischemia Detected by Ambulatory Electrocardiographic Monitoring in Chronic Stable Angio Pectoris, *Pra Kash, The American Journal of Cardiology*, vol. 80, Aug. 15, 1997, p. 421-425.

US 7,108,866 B1

Page 3

Kelly, J.G. et al., Pharmacokinetic Properties and Antihypertensive Efficacy of Once-Daily Diltiazem, *Journal of Cardio-Vascular Pharmacology*, 17:6:957-963, (1991).

Kohno, I. et al., Administration Time—Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hypertension Patients, *Chronobiology International*, 14(1), 71-84, (1997).

Leeuwenkamp, O.R. et al, A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets, *Eur. J. Clin. Pharmacol.*, (1994) 46:243-247.

Thiffault, J. et al., The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morning Against Bedtime, *Biopharmaceutics & Drug Disposition*, vol. 17, 107-115 (1996).

Zahirul, M. et al., Recent Trends and Progress in Sustained or Controlled Oral Delivery of Some Water Soluble Drugs: Morphine Salts, Diltiazem and Captopril, *Drug Development and Industrial Pharmacy*, US, New York, NY, vol. 21, No. 9, Jan. 1, 1995, pp. 1037-1070.

\* cited by examiner

U.S. Patent

Sep. 19, 2006

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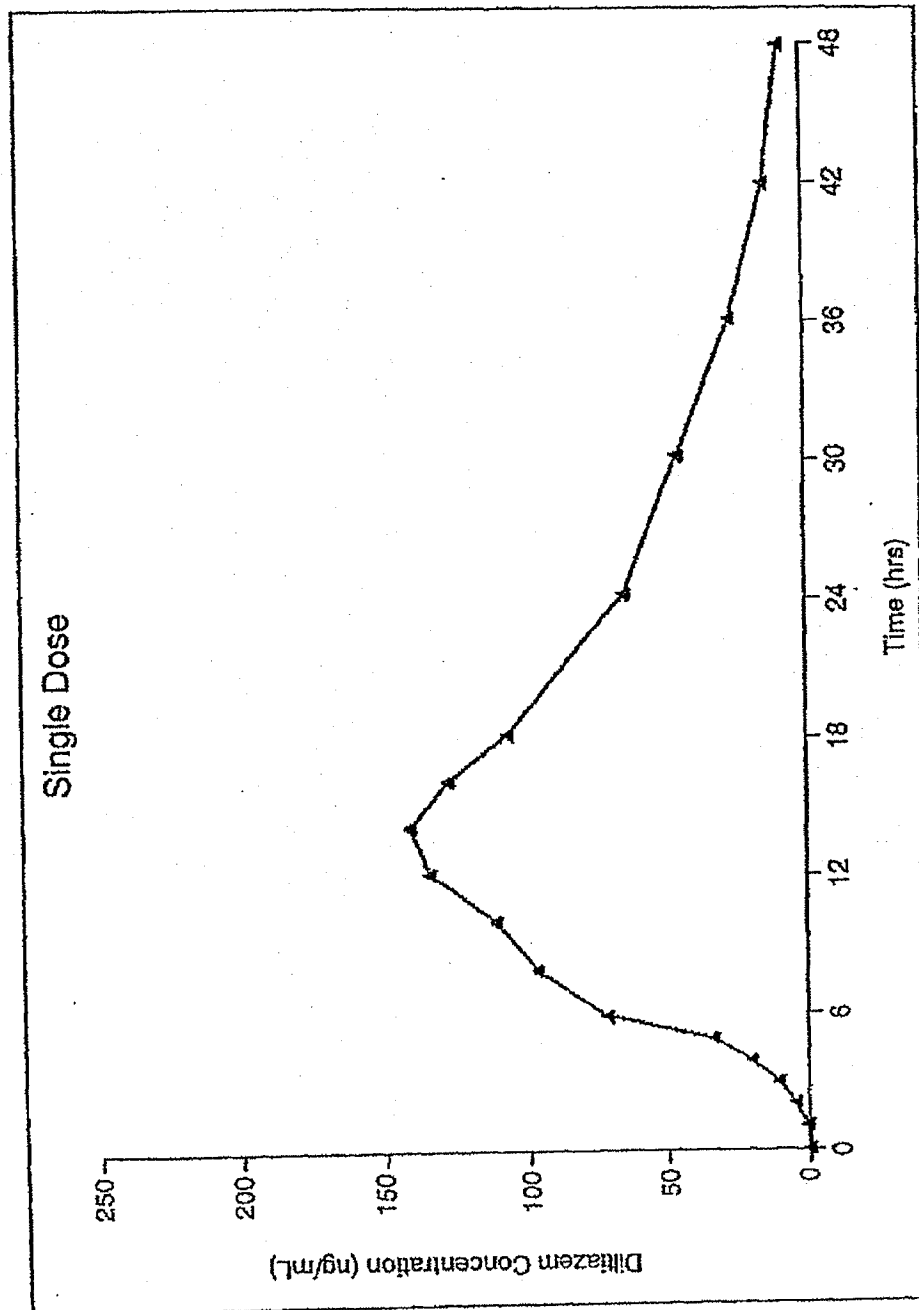


Fig. 1

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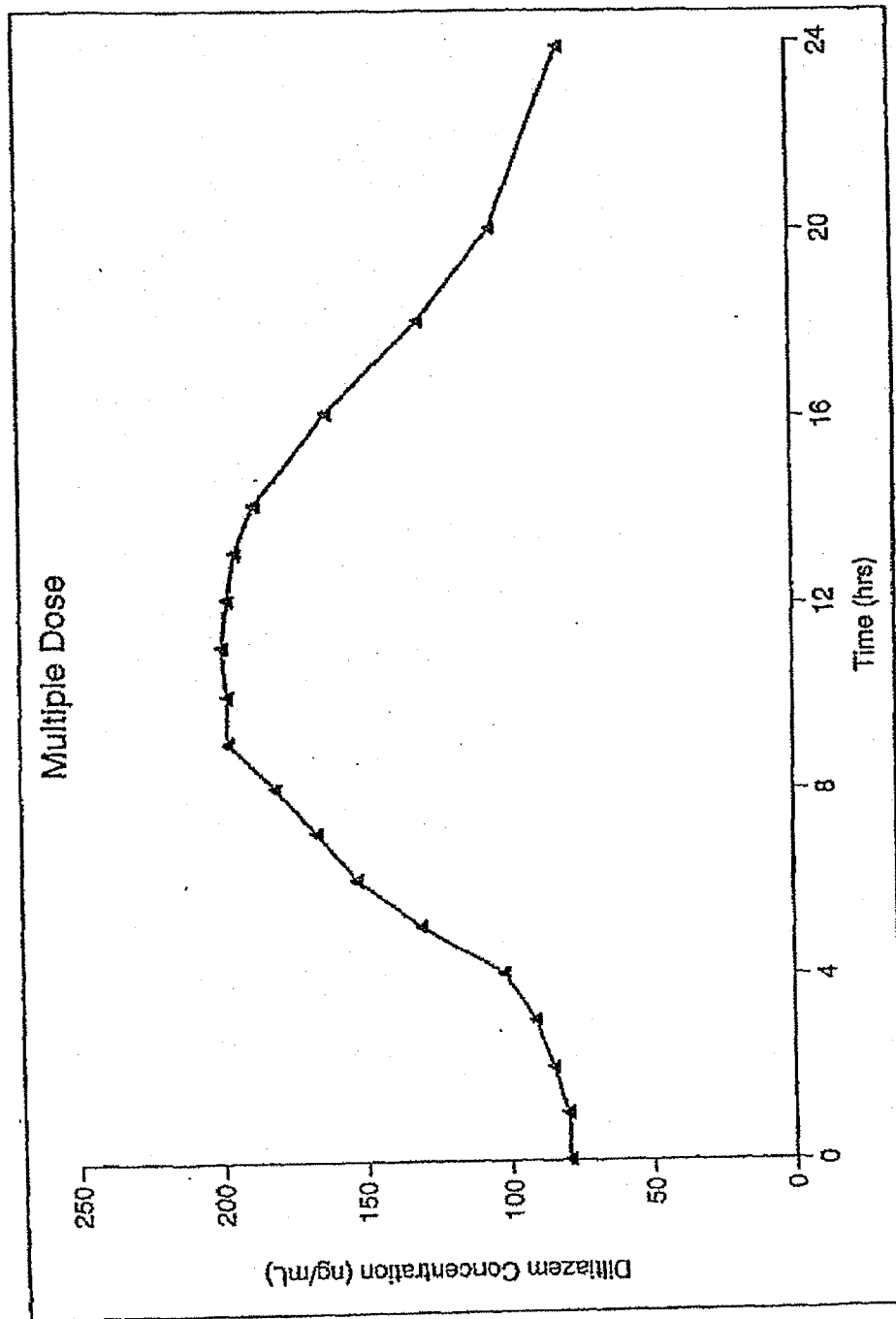


Fig. 2



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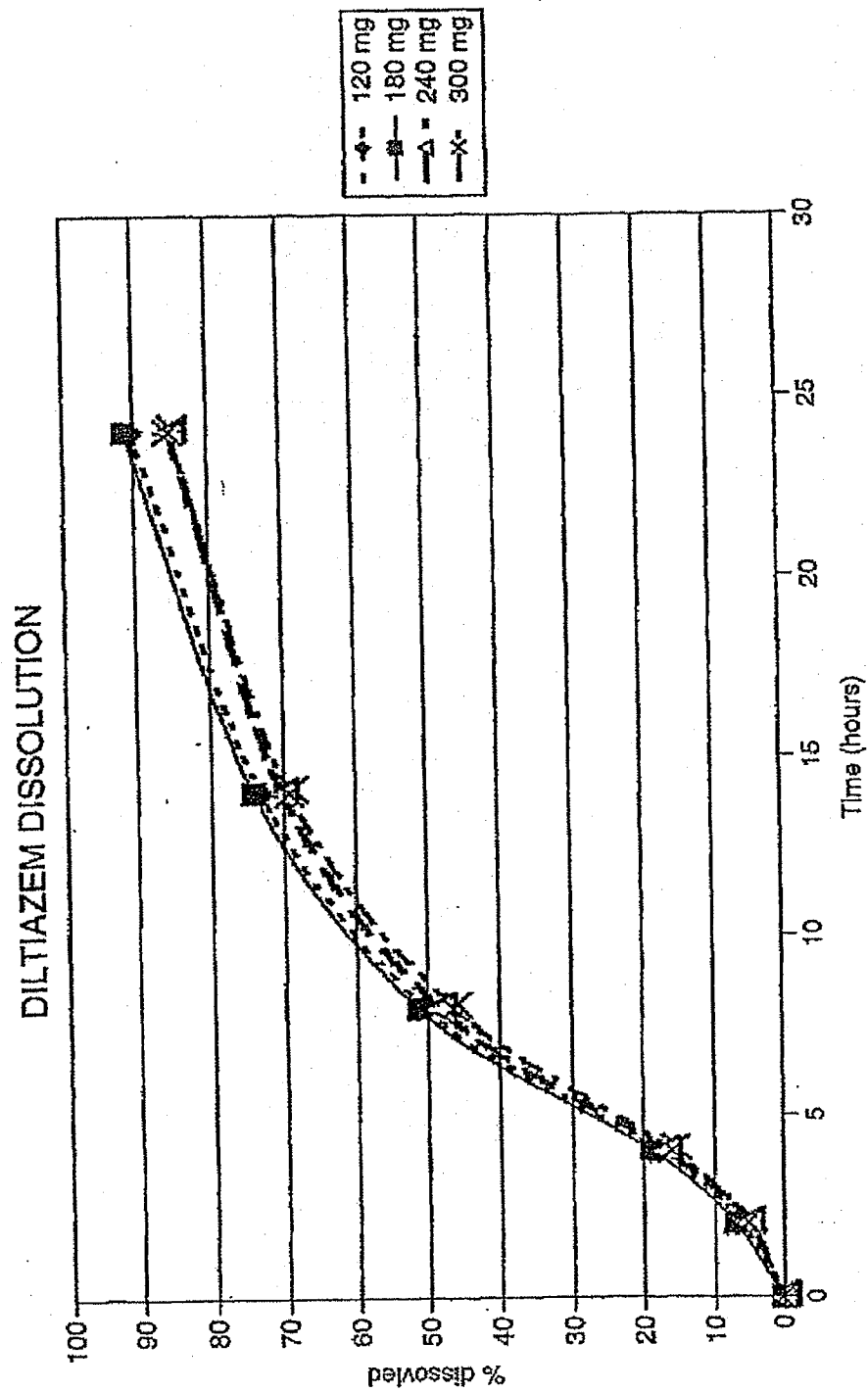


Fig. 3

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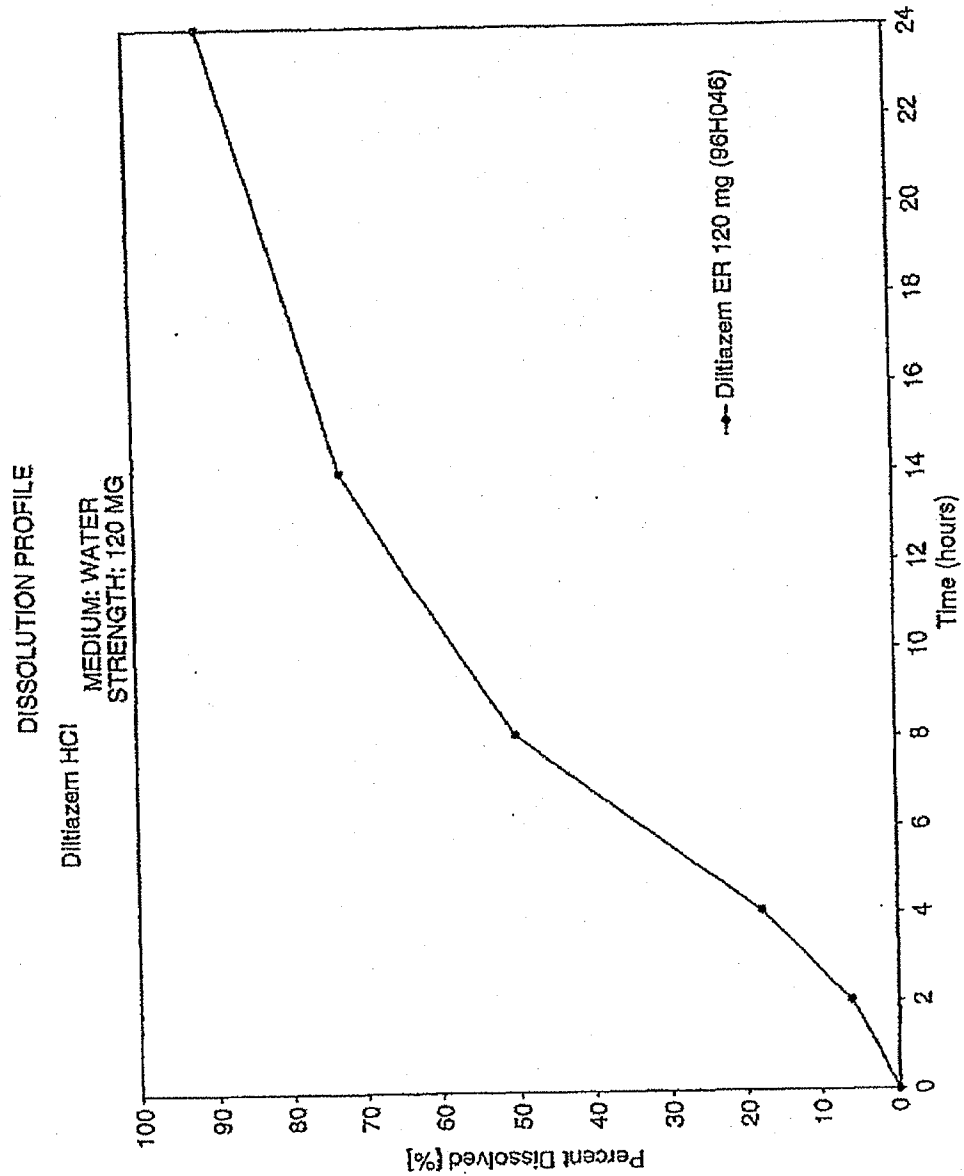


Fig. 4

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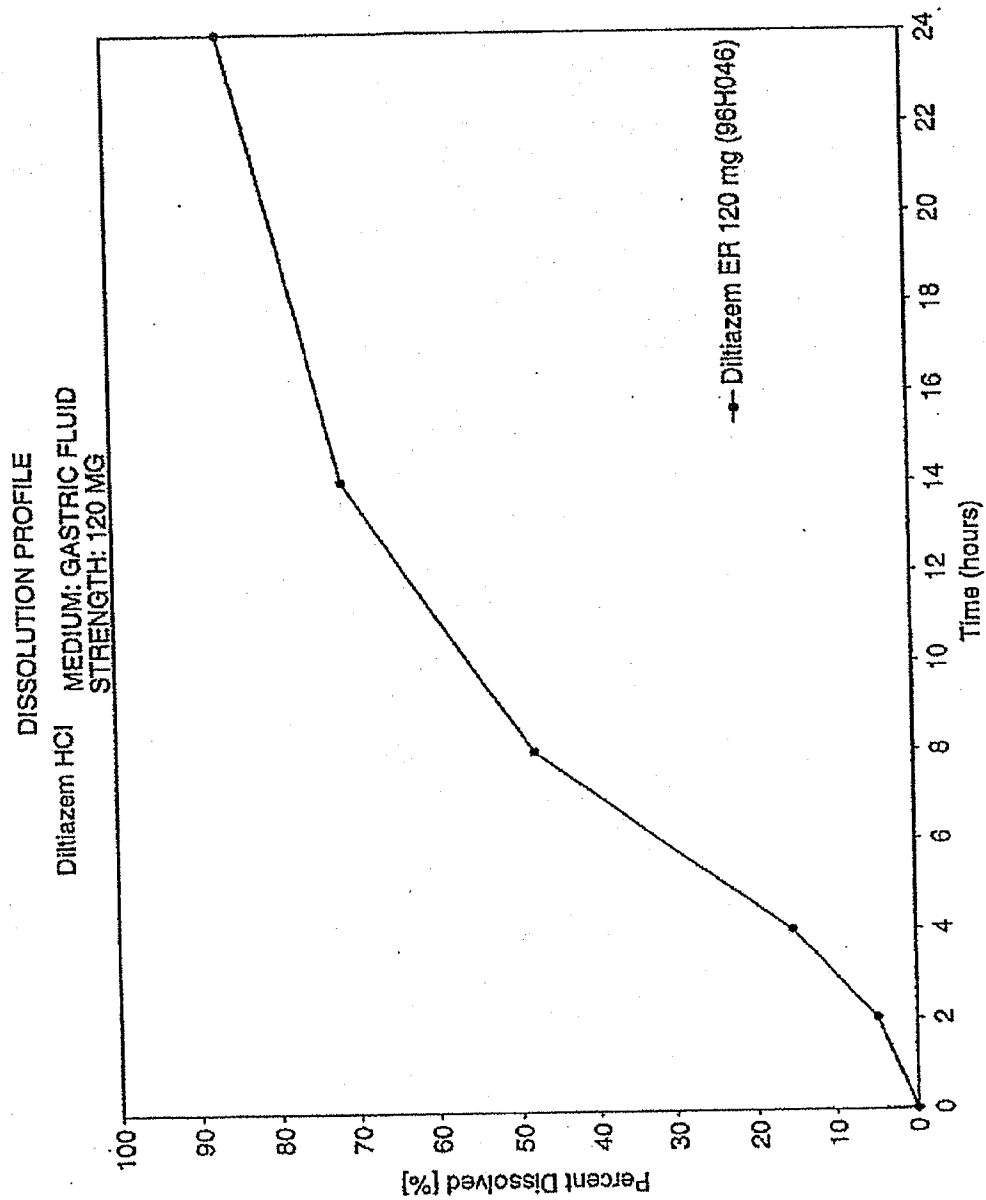


Fig. 5

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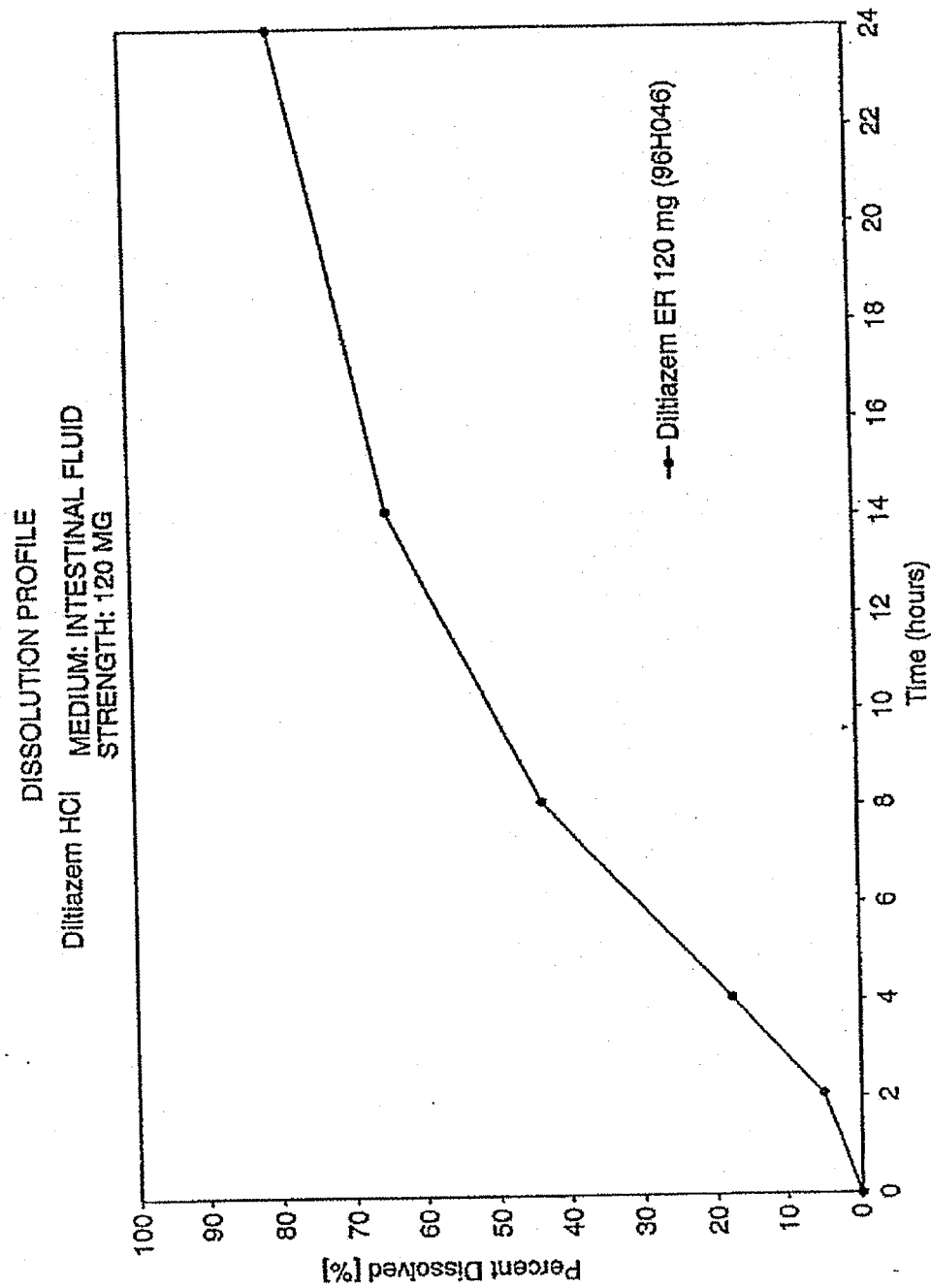


Fig. 6

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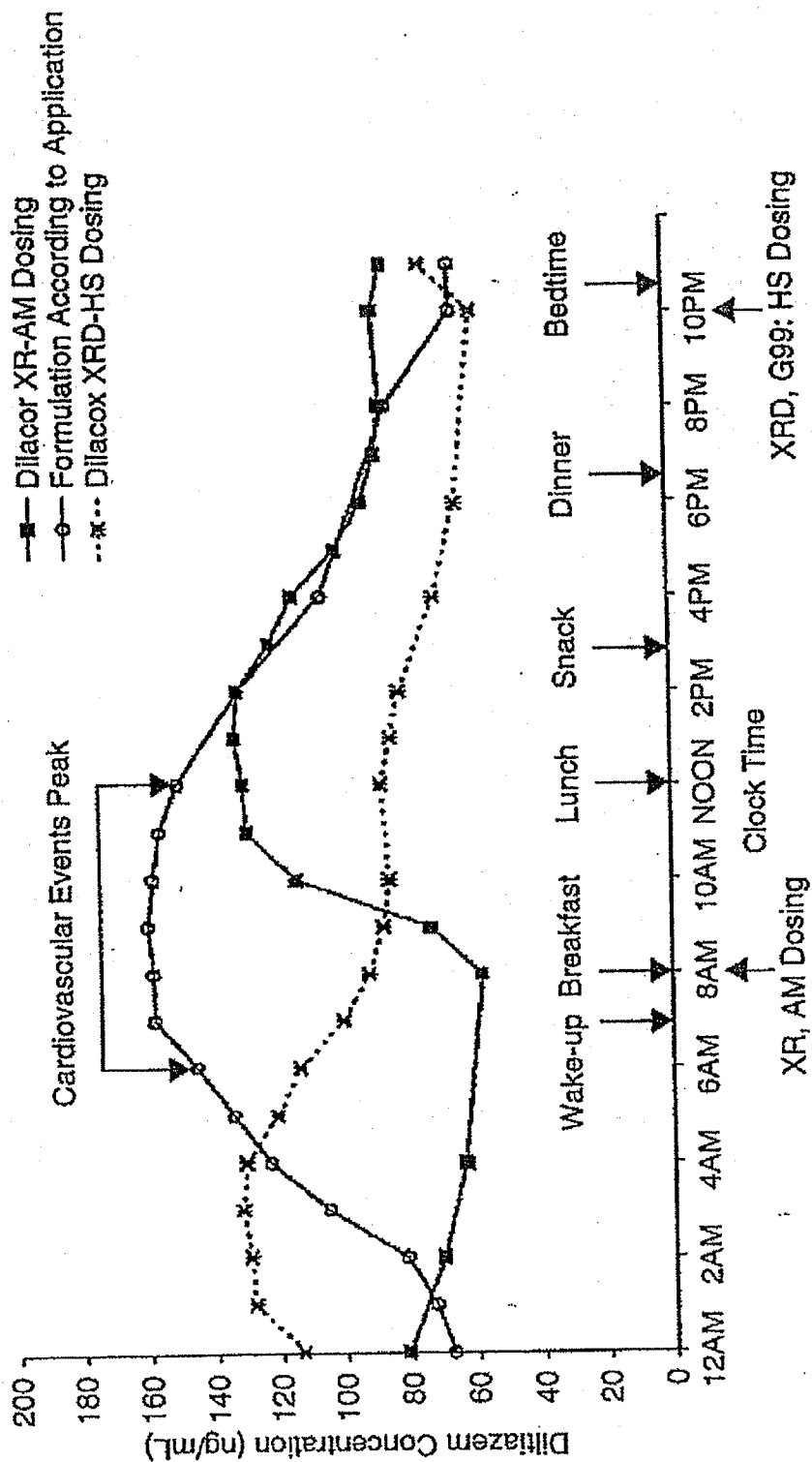


Fig. 7

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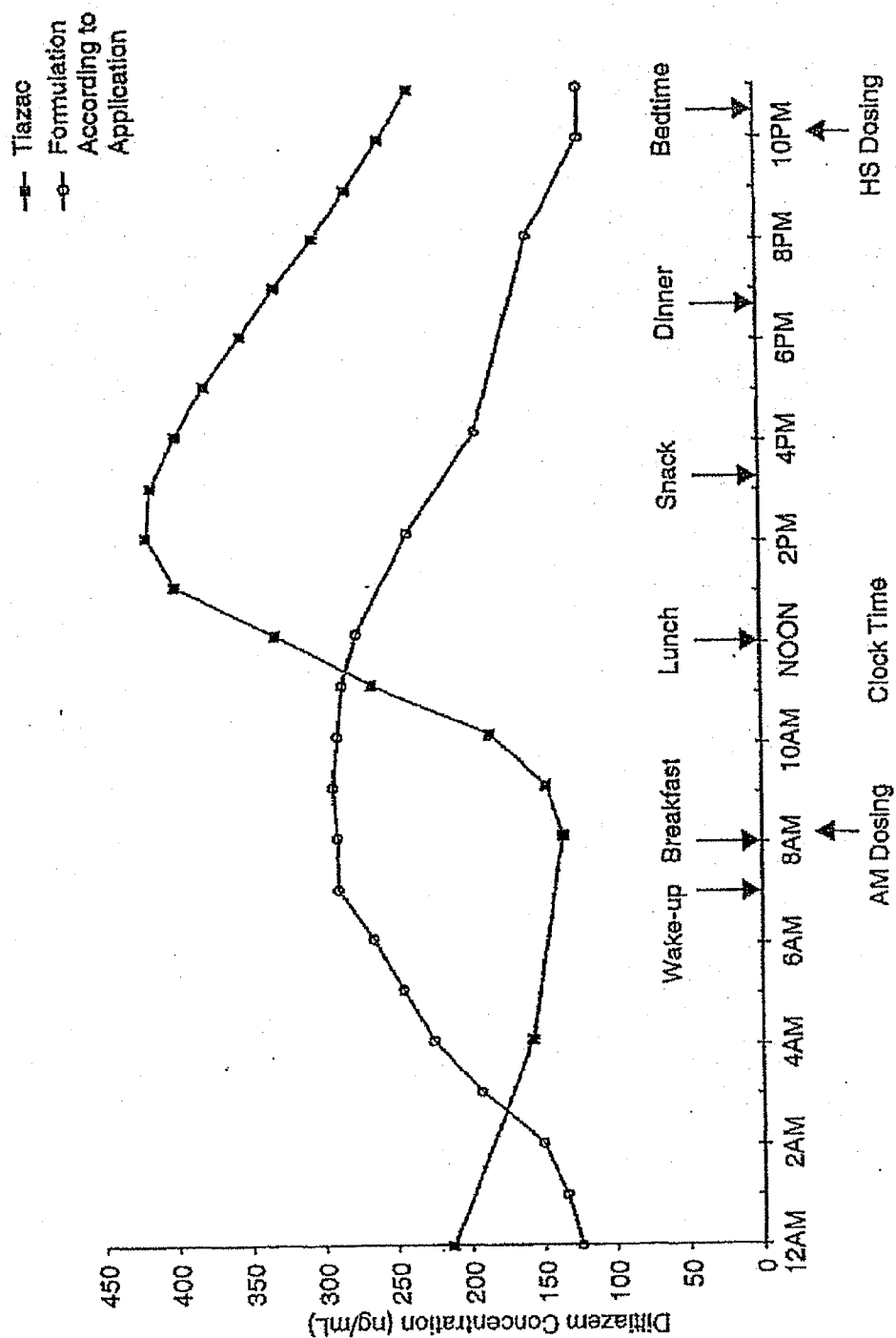


Fig. 8

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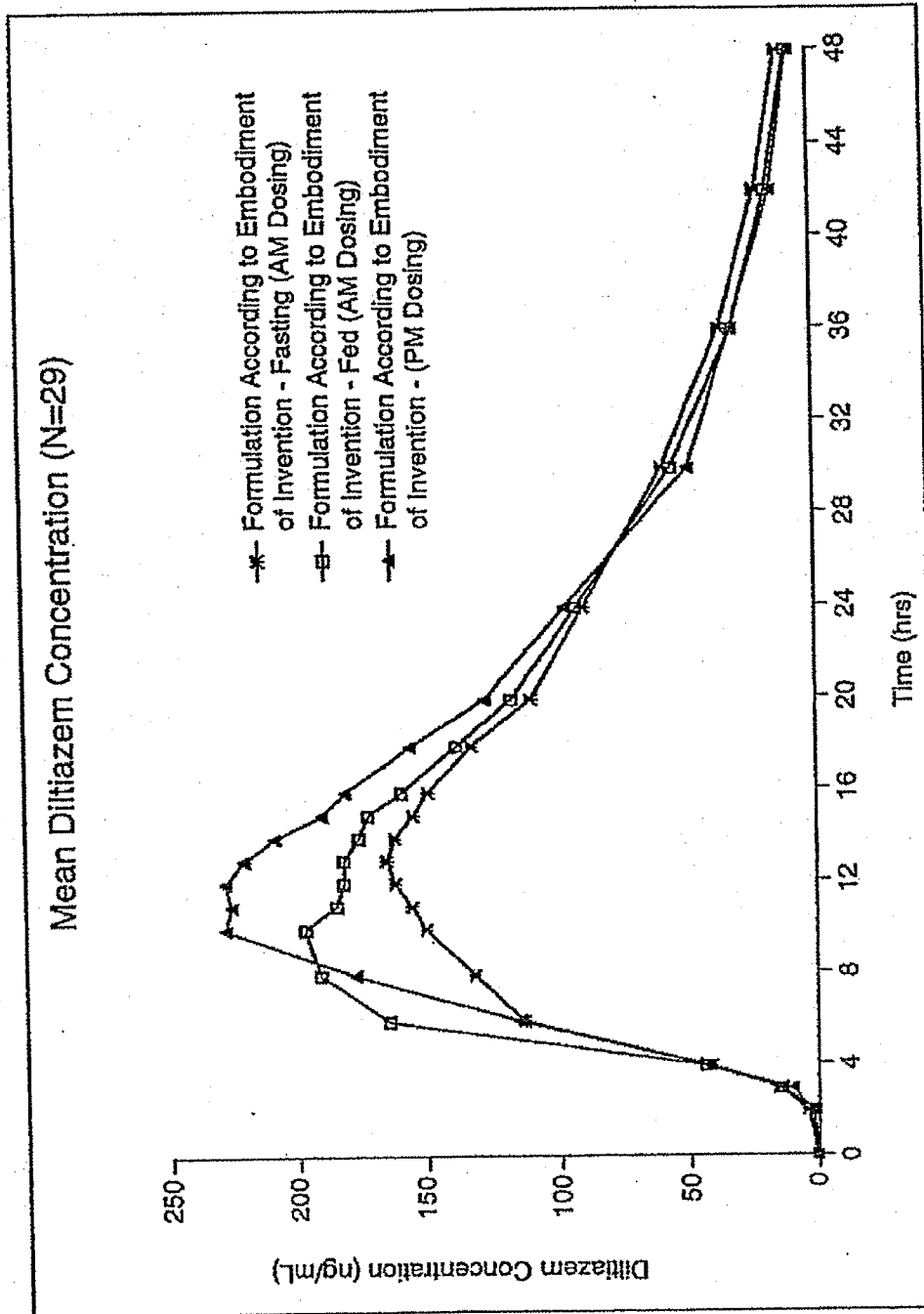


Fig. 9

A-1009

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## Diltiazem AUC1 PK Summary

## Formulation According to Embodiment of Invention

Subject	Morning Fasting		Morning Fed		Night Dosing		Morning	Night/Morning
	AUC1	Log AUC1	AUC1	Log AUC1	AUC1	Log AUC1	Fed/Fast Ratio	
2	1730.75	7.48	2647.15	7.88	1987.11	7.59	1.53	1.15
3	2712.88	7.91	2336.67	7.76	3249.94	8.09	0.86	1.20
4	2688.34	7.90	1907.61	7.55	2892.21	7.97	0.71	1.08
5	4192.37	8.34	4108.85	8.32	4702.33	8.46	0.98	1.12
6	3074.51	8.03	2887.98	7.97	3900.06	8.27	0.94	1.27
7	1629.81	7.40	1847.56	7.52	2723.36	7.91	1.13	1.67
8	841.10	6.85	1970.97	7.59	1835.11	7.51	2.09	1.95
9	3144.13	8.05	3462.59	8.15	2923.86	7.98	1.10	0.93
10	2074.94	7.64	2997.45	8.01	4028.83	8.30	1.44	1.94
11	3653.98	8.20	2771.53	7.93	3464.72	8.15	0.76	0.95
12	2684.22	7.90	3780.43	8.24	3141.47	8.05	1.41	1.17
13	3352.69	8.12	3751.85	8.23	3708.83	8.22	1.12	1.11
14	2988.61	8.00	3665.60	8.21	3141.05	8.05	1.23	1.05
15	6795.97	8.82	8204.22	9.01	7578.33	8.93	1.21	1.11
16	2873.70	7.95	4644.79	8.44	4192.09	8.34	1.62	1.46
17	4468.33	8.40	4222.55	8.35	3762.50	8.23	0.94	0.84
18	5654.29	8.64	5635.72	8.64	7159.38	8.88	1.00	1.27
19	4944.07	8.51	5107.44	8.54	4812.20	8.48	1.03	0.97
20	2988.73	8.00	2988.34	8.00	2791.23	7.93	1.00	0.93
21	2808.88	7.98	3314.12	8.11	4389.98	8.39	1.14	1.51
22	4270.43	8.36	3790.08	8.24	3631.01	8.20	0.89	0.85
23	6150.18	8.72	6092.56	8.71	7478.22	8.92	0.99	1.22
25	2926.46	7.98	5633.64	8.64	4839.10	8.48	1.93	1.65
26	3928.61	8.28	4614.43	8.44	4359.77	8.38	1.17	1.11
27	3637.94	8.20	4587.48	8.43	4063.15	8.31	1.26	1.12
28	4177.76	8.34	4945.31	8.51	6689.14	8.81	1.18	1.60
29	3609.69	8.18	2720.67	7.91	2163.20	7.68	0.75	0.60
30	4483.17	8.41	5222.54	8.56	5587.50	8.63	1.16	1.25
32	4058.04	8.31	3531.47	8.17	3082.87	8.03	0.87	0.76
Mean	3542.88	8.10	3910.40	8.21	4078.57	8.25	1.15	1.20
SD	1304.23	0.41	1431.24	0.36	1554.69	0.37	0.33	0.33
CV	36.81	5.08	36.60	4.43	38.12	4.46	28.23	27.33
Median	3352.69	8.12	3751.85	8.23	3762.50	8.23	1.12	1.12
Geo Mean	3292.83	8.09	3671.24	8.20	3818.30	8.24	1.11	1.16

## Fed/Fasting Ratio (Morning Dosing)

Ratio of Means	1.10	#
Ratio of Geo Means	1.11	#
Avg of Individual Ratio	1.15	#

## Night/Morning Ratio

Ratio of Means	1.15
Ratio of Geo Means	1.16
Avg of Individual Ratios	1.20

Fig. 9A



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Diltiazem Cmax PK Summary									
Formulation According to Embodiment of Invention									
Subject	Morning Fasting			Morning Fed			Night Dosing		
	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax
1	10.0	98.89	4.99	10.0	187.71	5.23	13.0	143.84	4.97
2	10.0	136.18	4.91	11.0	123.04	4.81	10.0	248.57	5.51
3	13.0	133.23	4.89	10.0	118.68	4.78	10.0	191.44	5.25
4	15.0	222.52	5.41	8.0	195.66	5.28	12.0	254.98	5.54
5	8.0	150.85	5.02	8.0	164.11	5.10	18.0	179.87	5.19
6	12.0	90.66	4.81	14.0	121.84	4.80	12.0	179.87	5.19
7	10.0	85.66	4.18	11.0	119.30	4.78	11.0	133.35	4.89
8	8.0	155.46	5.05	8.0	262.70	5.68	12.0	175.62	5.17
9	13.0	95.45	4.68	6.0	168.81	5.12	13.0	186.84	5.28
10	8.0	95.45	4.68	6.0	168.81	5.12	13.0	186.84	5.28
11	14.0	212.41	5.36	11.0	164.84	5.04	14.0	183.66	5.21
12	10.0	117.75	4.77	10.0	201.43	5.31	11.0	174.95	5.16
13	14.0	148.80	5.01	13.0	188.51	5.24	10.0	208.78	5.34
14	13.0	139.54	4.94	8.0	205.35	5.32	13.0	187.32	5.23
15	16.0	266.48	5.69	15.0	330.93	5.80	13.0	450.34	6.11
16	13.0	134.55	4.90	8.0	281.74	5.84	10.0	238.10	5.46
17	12.0	224.65	5.41	10.0	244.82	5.50	14.0	203.51	5.32
18	14.0	281.88	5.84	8.0	308.26	5.73	13.0	478.11	6.17
19	15.0	227.89	5.43	11.0	262.82	5.67	13.0	231.49	5.44
20	14.0	137.54	4.82	10.0	175.76	5.17	10.0	173.83	5.16
21	13.0	164.75	5.10	13.0	187.63	5.28	13.0	301.72	5.71
22	16.0	182.82	5.21	11.0	207.19	5.33	10.0	247.08	5.51
23	18.0	269.97	5.80	10.0	340.21	5.83	10.0	600.82	6.22
25	10.0	165.06	5.11	8.0	322.66	5.78	10.0	263.27	5.57
26	13.0	208.19	5.34	10.0	237.50	5.47	10.0	235.12	5.46
27	27.0	162.47	5.09	8.0	255.85	5.54	10.0	170.18	5.14
28	13.0	218.59	5.39	11.0	288.10	5.48	11.0	384.02	5.95
28	13.0	215.15	5.37	13.0	180.73	5.08	12.0	128.94	4.87
29	14.0	242.06	5.48	12.0	244.53	5.50	10.0	336.64	5.82
30	14.0	303.43	5.72	15.0	204.09	5.32	11.0	231.33	5.44
Mean	12.6	178.45	5.12	10.2	215.53	5.33	11.6	242.46	5.42
SD	2.5	51.55	0.37	2.5	84.85	0.31	1.6	98.98	0.36
CV	19.8	34.86	7.32	24.3	30.08	0.83	14.1	40.82	0.58
Median	13.0	164.75	5.10	10.0	204.09	5.32	11.0	208.78	5.34
Geo Mean	12.3	167.47	5.11	9.9	208.00	5.32	11.5	228.63	5.41
Fed/Fasting Ratio (Morning Dosing)									
Ratio of Means			1.21	Night/Morning Ratio			Ratio of Means		
Ratio of Geo Means			1.23	Ratio of Geo Means			Ratio of Geo Means		
Avg of Individual Ratios			1.29	Avg of Individual Ratios			Avg of Individual Ratios		
Morning Fed/Fasting Ratio			1.80	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.48	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.90	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.61	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.89	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.44	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.88	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.15	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.09	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.19	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.34	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.98	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.82	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			2.03	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.88	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.13	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.75	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			2.06	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.73	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			0.86	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.71	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.48	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.26	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.38	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.47	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.34	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.24	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.68	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			2.08	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.75	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.09	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			0.91	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.09	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.70	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.15	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.02	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.28	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.36	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.20	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.83	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.34	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.35	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.26	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.65	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.94	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.59	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.14	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.43	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.57	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.05	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.08	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.76	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.75	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			0.60	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.01	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.39	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.87	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			0.76	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			1.29	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			1.41	Night/Morning Ratio			Night/Morning Ratio		
Morning Fed/Fasting Ratio			0.40	Morning Fed/Fasting Ratio			Morning Fed/Fasting Ratio		
Night/Morning Ratio			0.39	Night/Morning Ratio			Night/Morning Ratio		

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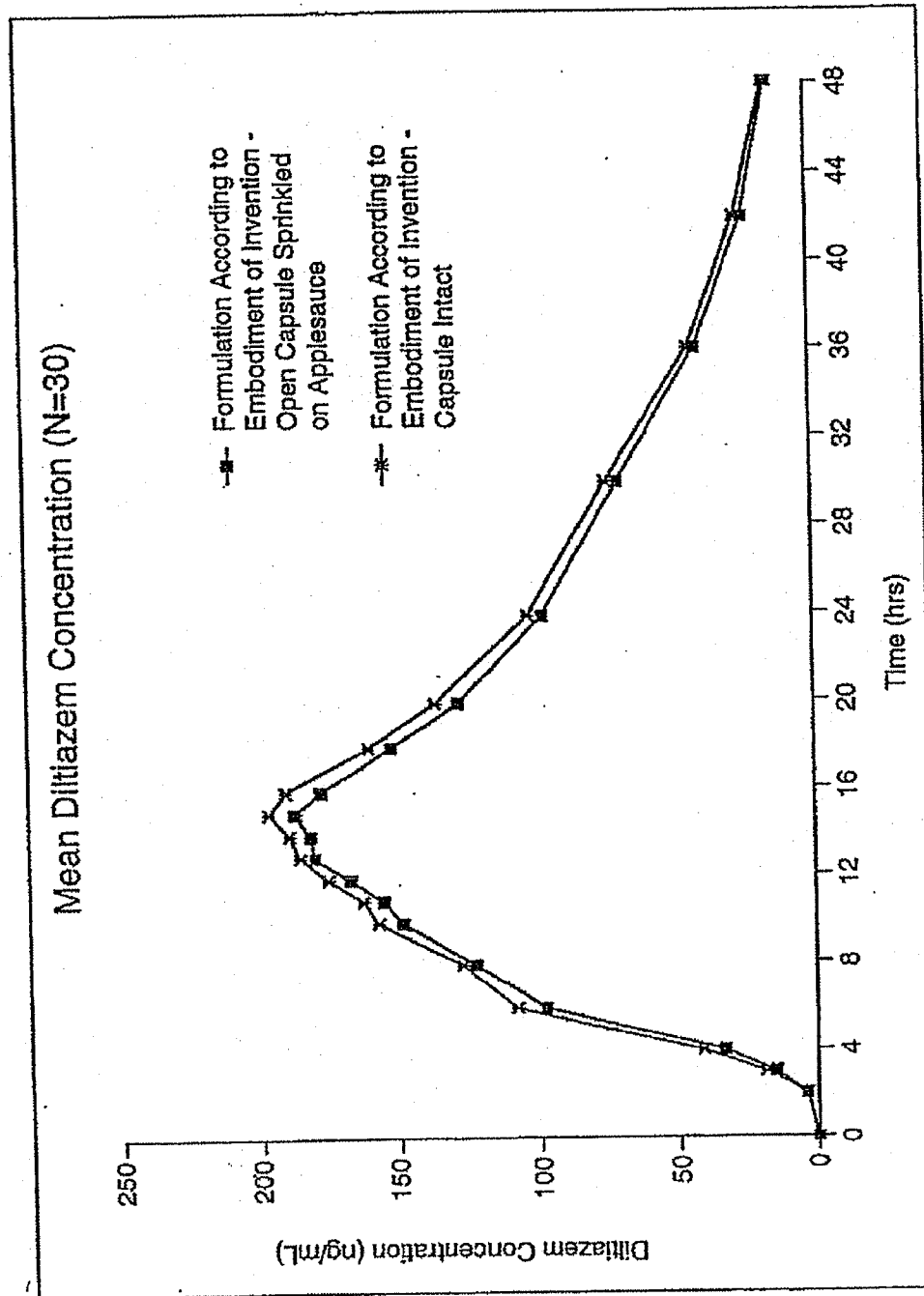


Fig. 10

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PK Summary (N=30)

Diltiazem PK

Open Capsule Sprinkled on Applesauce / Capsule Intact

AUCt

Ratio of Means %  
Ratio of Geo Means %  
Avg of Individual Ratios %  
90% C.I.  
Intra-CV

94.16  
93.98  
96.03  
88%-99%  
13.47%

Cmax

Ratio of Means %  
Ratio of Geo Means %  
Avg of Individual Ratios %  
90% C.I.  
Intra-CV

93.35  
93.00  
95.73  
86%-99%  
16.07%

Tmax

Open Capsule Sprinkled on Applesauce  
Capsules Intact

Mean

13.7 hours  
13.5 hours

Fig. 10A

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## Diltiazem AUC Results

## Formulation According to Embodiment of Invention

Subject	Open Capsules Sprinkled on Applesauce (A)		Capsule Intact (B)		(A:B) Ratio
	AUCt	Log Cmax	AUCt	Log Cmax	
1	3937.18	8.28	3251.62	8.09	1.21
2	3792.89	8.24	5502.18	8.61	0.69
3	1616.35	7.39	2358.22	7.77	0.69
4	8209.44	9.01	7954.29	8.98	1.03
5	2171.26	7.68	2452.78	7.80	0.89
6	5710.90	8.65	7082.30	8.87	0.81
7	1983.56	7.59	2624.03	7.87	0.76
8	3862.46	8.26	3114.53	8.04	1.24
9	6069.65	8.71	4585.60	8.43	1.32
10	3907.33	8.27	6393.14	8.76	0.61
11	3842.58	8.25	4292.30	8.36	0.90
12	4873.82	8.49	6493.87	8.78	0.75
13	2707.85	7.90	3922.90	8.27	0.69
14	2553.27	7.85	2159.88	7.68	1.18
15	2042.47	7.62	2902.70	7.97	0.70
16	4550.14	8.44	4769.32	8.47	0.98
17	3705.72	8.22	3464.89	8.15	1.07
19	7881.69	8.97	6851.45	8.83	1.15
21	6151.00	8.72	6292.65	8.75	0.98
22	2138.64	7.67	1933.52	7.57	1.11
23	3983.50	8.29	5177.74	8.55	0.77
24	3939.51	8.28	3517.56	8.17	1.12
25	2318.36	7.75	2016.26	7.61	1.15
27	2061.09	7.63	1928.02	7.56	1.07
28	2871.31	7.96	3312.87	8.11	0.87
29	4305.14	8.37	3559.57	8.18	1.21
30	3190.17	8.07	3565.88	8.18	0.89
31	3422.16	8.14	3012.17	8.01	1.14
33	4906.47	8.50	5206.52	8.56	0.94
34	2969.19	8.00	3255.28	8.09	0.91
Mean	3859.17	8.17	4098.47	8.24	0.96
SD	1664.90	0.42	1708.24	0.41	0.20
CV	43.14	5.10	41.68	5.03	20.69
Median	3817.74	8.25	3538.57	8.17	0.96
Geo Mean	3546.16	8.16	3773.43	8.23	0.94
Test/Ref Ratio					
Ratio of Means %		94.16			
Ratio of Geo Means %		93.98			
Avg of Individual Ratios		0.96			
90% C.I.		88%-99%			
Intra-CV		13.47%			

Fig. 10B

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## Diltiazem Cmax Results

## Formulation According to Embodiment of Invention

Subject	Open Capsule Sprinkled on Applesauce (A)			Capsule Intact (B)			(A:B) Ratio
	Tmax	Cmax	Log Cmax	Tmax	Cmax	Log Cmax	
1	13.0	184.35	5.22	13.0	228.99	5.43	0.81
2	14.0	192.44	5.26	12.0	286.72	5.66	0.67
3	13.0	103.87	4.64	12.0	127.07	4.84	0.82
4	10.0	372.93	5.92	8.0	298.05	5.70	1.25
5	14.0	107.71	4.68	16.0	147.84	5.00	0.73
6	13.0	244.87	5.50	15.0	315.48	5.75	0.78
7	14.0	115.23	4.75	16.0	135.27	4.91	0.85
8	13.0	257.26	5.55	15.0	179.11	5.19	1.44
9	8.0	232.12	5.45	10.0	194.37	5.27	1.19
10	16.0	172.20	5.15	15.0	281.81	5.64	0.61
11	13.0	177.41	5.18	8.0	181.17	5.20	0.98
12	13.0	225.55	5.42	10.0	327.23	5.79	0.69
13	15.0	135.86	4.91	15.0	213.37	5.36	0.64
14	15.0	154.65	5.04	14.0	135.94	4.91	1.14
15	12.0	114.81	4.74	15.0	181.80	5.20	0.63
16	15.0	294.21	5.68	13.0	296.58	5.69	0.99
17	15.0	187.32	5.23	15.0	183.62	5.21	1.02
19	16.0	385.36	5.95	15.0	376.57	5.93	1.02
21	15.0	318.06	5.76	10.0	276.15	5.52	1.15
22	14.0	114.40	4.74	14.0	97.24	4.58	1.18
23	12.0	260.20	5.56	12.0	346.74	5.85	0.75
24	14.0	211.61	5.35	16.0	202.88	5.31	1.04
25	14.0	155.98	5.05	15.0	125.66	4.83	1.24
27	16.0	79.66	4.38	16.0	67.35	4.21	1.18
28	16.0	124.76	4.83	16.0	165.01	5.11	0.76
29	15.0	225.58	5.42	10.0	164.02	5.10	1.38
30	14.0	168.54	5.12	15.0	165.41	5.11	1.01
31	15.0	134.14	4.90	14.0	136.19	4.91	0.99
33	13.0	282.10	5.64	16.0	275.33	5.62	1.02
34	10.0	118.88	4.78	15.0	155.15	5.04	0.77
Mean	13.7	195.00	5.19	13.5	208.90	5.27	0.96
SD	1.9	80.09	0.41	2.5	80.27	0.41	0.23
CV	13.8	41.07	7.83	18.3	38.43	7.73	24.25
Median	14.0	180.88	5.20	15.0	182.71	5.21	0.99
Geo Mean	13.5	180.09	5.18	13.3	193.65	5.25	0.93
Test/Ref Ratio							
Ratio of Means %			93.35				
Ratio of Geo Means %			93.00				
Avg of Individual Ratios			0.96				
90% C.I.			86%-99%				
Intra-CV			16.07%				

Fig. 10C

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# CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

This application is a continuation-in-part application of U.S. patent application Ser. No. 09/465,338 filed Dec. 17, 1999 now abandoned claiming priority from Canadian Patent Application No. 2,292,247 filed Dec. 10, 1999. This application also claims priority from a Canadian Patent Application filed May 4, 2000.

## FIELD OF INVENTION

This invention relates to once daily preparations comprising Diltiazem and pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening administration to patients suffering hypertension and/or angina. This invention also relates to a method for evening administration of such once daily preparations to patients for the treatment of the patients' hypertension and/or angina.

## BACKGROUND OF THE INVENTION

Diltiazem, a benzothiazepine, is an orally active calcium channel blocker (calcium-antagonist) with relatively high selectivity for vascular smooth muscle that is effective in the treatment of hypertension and angina pectoris. Today, persons having these conditions take prescribed once daily preparations of Diltiazem generally to maintain constant levels of the drug in the body over a 24-hour period. Until recently the timing of the taking of the medicine wasn't considered an important consideration by the medical community. Doctors generally did not take into account the natural circadian variation in the body's physiological functions. Researchers have now found that the timing of the taking of a medicine can affect the way the human body responds to the medicine. The science of treating the human body taking into account the natural circadian variation is Chronotherapeutics. Chronotherapeutics relies on the practice of delivering the correct amount of medication to the correct site of action at the most appropriate time period for the particular disease or condition. In man, blood pressure does not remain constant during day and night. Early in the morning blood pressure begins to rise from the low levels reached during sleep. Increases in blood pressure are accompanied by increases in heart rate caused by the chemicals generated by the body and delivered into the blood stream. Epidemiological studies have indicated that the greatest incidence of heart problems such as stroke, heart attack, myocardial ischemia and sudden cardiac death occur during the early morning waking hours when the blood pressure is rising in response to the natural circadian rhythm. After normally rising in the morning, blood pressure remains elevated during the day until generally early evening when it starts to fall to its lowest level during sleep.

In one study, evening medication with Diltiazem for treatment of hypertension for effect the next morning has been stated to be more efficacious than other dosage schedules. *Administration Time-Dependent Effects of Diltiazem on The 24-Hour Blood Pressure Profile of Essential Hypertension Patients*, Isao Kohno et al. (Chronobiology International 14(1), 71-84, (1997). In the report of the study, Herbesser R<sup>TM</sup> (200 mg) was identified as the Diltiazem preparation. Herbesser R<sup>TM</sup> is a Diltiazem formulation comprising a mixture of immediate release diltiazem—containing microspheres and sustained release diltiazem—containing coated microspheres. According to the report, following

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a single dose (200 mg) administration, the time of peak plasma diltiazem concentration occurred at 12.5 hours after administration. The peak plasma diltiazem concentration C<sub>max</sub> in the persons studied was 107 mg/ml. Following multiple dosages of 200 mg Diltiazem given over 7 days, the time of peak plasma diltiazem concentration (C<sub>max</sub>) was at 10 hours after administration. C<sub>max</sub> was 154 mg/ml.

However a careful review of the report shows inconsistencies which cannot support the authors' conclusions. Particularly at page 80, the best results shown in the graph are with respect to morning treatment with this formulation. Moreover at page 82, the authors themselves acknowledge the study cannot lead to reliable conclusions "because the number of patients was too small". Further, an immediate release portion of the dosage in the order of 15% is not desirable for evening administration. When the blood pressure is naturally at its lowest, not only is there no need for further reduction at that time, but such reduction can harm the patient. Particularly, if the blood pressure is reduced below a minimum the patient is put at a greater risk for cardiovascular accidents including stroke. Further, the 15% immediate release diltiazem is no longer available when needed.

In *A comparative study of the steady-state pharmacokinetics of immediate-release and controlled-release diltiazem tablets*, O. R. Leeuwenkamp et al., Eur. J. Clin. Pharmacol (1994) 46:243-247, controlled release properties and relative systemic availabilities of two dosages of the same controlled release diltiazem tablet formulation were studied by comparing them as steady state with those of an immediate release formulation. In the testing, the diltiazem plasma concentration increased slowly from about 6 hours after the evening dose of both CR tablets (Diltiazem CR 90 mg and Diltiazem CR 120 mg) resulting in relatively high plasma concentrations in the early morning hours. The clinicians concluded that twice-daily treatment with diltiazem CR tablets can replace thrice-daily treatment with a conventional diltiazem IR tablet. According to the clinicians "The early morning rise of the diltiazem plasma concentration, which might lead to a lower incidence of ischemic events, may be an important clinical advantage of both CR tablets."

On Apr. 22, 1998, Searle Canada announced that its Chronovera (R) (controlled onset extended-release verapamil) a high blood pressure medication was now available in Canada. Chronovera (R) was, according to Searle Canada, specifically designed to work with the body's natural circadian variations and was designed to be taken once-a-day just before bedtime. Chronovera provided 24-hour blood pressure control but was designed to deliver peak concentrations of verapamil in the morning when the blood pressure, heart rate and incidence of cardiovascular events were highest. According to Searle Canada, simply changing the time you take the drug your physician has prescribed will not provide the same safety and effectiveness that is designed specially for chronotherapy using verapamil. According to Searle Canada, its Chronovera (R) is unlike traditional medications including extended-release (XL) and sustained-release (SR) formulations which are usually prescribed in doses that maintain relatively constant levels of the drug in the body over a 24-hour period or attempt to maintain relatively constant levels of the drug in the body over a 24-hour period. According to Searle Canada, the prior formulations do not take into account the natural circadian variations in the body's physiological functions.

Sustained-release, once-daily diltiazem formulations have been taught which may be considered the traditional medi-

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cation (according to Searle Canada). They appear not to give the benefits meant to be achieved by chronotherapy.

For example, in *Pharmacokinetic Properties and Antihypertensive Efficacy of Once-Daily Diltiazem*, J. G. Kelly et al., *Journal of Cardio-Vascular Pharmacology*, 17:6:957-963, (1991), the controlled-release formulation of diltiazem released a proportion of the diltiazem relatively rapidly with the remainder released over a period extending to 24-hours. During in vitro dissolution testing 15% of the diltiazem in the dosage form was released in the first two hours, 54% was released in the first six hours, 89% in the first 13 hours and all of the remainder was released between 13 and 24 hours after administration. The diltiazem capsules contained either 120 mg or 240 mg of diltiazem. It should be noted that no difference is shown between the placebo and dosages in the article at wake-up (between 5:00 a.m. and 8:00 a.m.).

U.S. Pat. No. 4,960,596 discloses slow release 12 hour diltiazem formulations whose dissolution, when measured in accordance with United States Pharmacopoeia 21, purports to be within broad limits (between 5% and 35% after one hour, between 15% and 40% after two hours, between 20% and 50% after three hours, between 30% and 75% after four hours, between 40% and 80% after six hours and between 55% and 95% after eight hours). The examples in the patent, however, provide more specific range limitations specifying range limitations for the formulations exemplified such as at column 4, lines 8-10 and column 5, lines 60-62. In the first series of examples the release into aqueous medium was measured using the method of USP No. 21 of 10%-20% after one hour, 30%-35% after four hours and 60%-75% after eight hours. In the later examples, the release into aqueous medium was measured using the method of USP No. 21 at 15%-35% after one hour, 55%-75% after four hours, 75%-95% after eight hours. These formulations were, however, twice a day (b.i.d.) formulations.

A series of patents have issued to Elan Corporation p.l.c. involving controlled absorption diltiazem pellet formulations for oral administration in which each pellet has a core comprising diltiazem or a pharmaceutically acceptable salt thereof in association with a specified organic acid covered by an outer membrane which permits release of diltiazem from aqueous medium in accordance with U.S. Pharmacopoeia XX (Paddle Method) in buffered media at pH 1.5, pH 4.0 and pH 7.0. These are U.S. Pat. Nos. 4,721,619; 4,891,230; 4,894,240; 4,917,899; 5,002,776; 5,219,621; 5,336,504; 5,364,620 and 5,616,345.

In U.S. Pat. No. 4,721,619, dissolution rates of the pellets of examples are found at column 4, lines 41-49 and column 5, lines 5-12. The formulations, however are for 12 hour. The formulations of U.S. Pat. No. 4,891,230 are also for administration every 12 hours.

U.S. Pat. No. 4,894,240 purports to provide formulations for once-daily administration and specifies a general dissolution pattern at column 2, lines 43-52 and a more restricted dissolution pattern at column 3, lines 3-12. The dissolution rates are determined according to U.S. Pharmacopoeia XXI in 0.05M KCl at pH 7.0 and at 100 r.p.m. The examples of the patent, however, provide a more limited dissolution pattern under U.S. Pharmacopoeia XXI (Paddle Method) at column 7, lines 30-34 and 47-51, at column 8, lines 16-20, 32-36 and 49-53 and at column 8, line 66-column 9, line 5. Similar examples are provided at columns 9, 10, 11 and 12. Nothing is taught with respect to formulations suitable as chronotherapeutics.

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U.S. Pat. Nos. 4,917,899, 5,364,620 and 5,616,345 are to the same effect. So are the remaining Elan patents. Nothing in these patents teach formulations suitable as chronotherapeutics.

U.S. Pat. No. 5,529,790 purports to teach a delayed sustained-release pharmaceutical preparation in which a water-soluble drug core is surrounded by a hydratable diffusion barrier which delays drug release for about two to ten hours. While diltiazem hydrochloride dissolution patterns were provided in accordance with the U.S.P. basket dissolution method specified, no Cmax or the timing of the maximum blood levels is provided. The dissolution rates of the active are not appropriate for a suitable chronotherapeutic (see also U.S. Pat. Nos. 5,376,384 and 5,478,573).

U.S. Pat. Nos. 5,288,505 and 5,529,791 relate to extended-release galenical formulations of diltiazem or pharmaceutically acceptable salts thereof which comprise beads in which the active ingredient is in association with a wetting agent and which beads are coated by a microporous membrane. The Cmax of some formulations given in the patents provide for a Cmax after about 8-12 hours. Where the dosing of the formulations of the patents yields maximum diltiazem blood plasma levels (Cmax) of about 145 ng/ml, the Cmax is at about or less than 8 hours.

The applicants are also aware of a formulation marketed under the trade mark Tiazac™ a diltiazem HCl 24-hour sustained-release formulation based on teachings of U.S. Pat. Nos. 5,529,791 and 5,288,505.

Following chronic administration of Tiazac (240 mg once daily), the average peak plasma Diltiazem concentration (Cmax) is 183 ng/ml (multiple dosage) which occurred after about 7 hours past dose administration. Tiazac™ provides a bioavailability of approximately 59% of the total Diltiazem in the first 12 hours and 41% in the second 12 hours (after 12 hours, 59%; after 16 hours 77% and after 20 hours 90%).

In an article entitled *Effect of Morning Versus Evening Dosing of Diltiazem on Myocardial Ischemia Detected by Ambulatory Electrocardiographic Monitoring in Chronic Stable Angio Pectoris*, PRA KASH, C. Deedwanian et al., *The American Journal of Cardiology*, Vol. 80, Aug. 15, 1997, p. 421-425, the authors compare a.m. and p.m. dosing without using an appropriate dosage form for p.m. The Tmax is achieved between 2-6 hours at steady state.

In an article *The Influence of Time Administration on the Pharmacokinetics of a Once A Day Diltiazem Formulation: Morning Against Bedtime*, Jean Thiffault et al., *Biopharmaceutics & Drug Disposition*, Vol. 17, 107-115 (1996), the once-a-day diltiazem formulation given at 2200 hours for seven days gave according to the article "significantly higher plasma concentrations of diltiazem in the early morning hours when the incidence of cardiovascular events is higher". The diltiazem dosages comprise 240 mg taken at 10:00 p.m. (22:00 hours) and maximum concentrations (Cmax) were achieved of 120 ng/ml after about six-eight hours of dosing. Unfortunately, the proposed system covers only the period from 2:00 a.m. to 8:00 a.m. To be a true chronotherapeutic, the time period covered should be between about 6:00 a.m. and noon. Moreover, this formulation when given at night leads to significantly lower bioavailability than if given in the morning.

It is therefore an object of this invention to provide diltiazem preparations suitable for once-a-day administration in the evening for providing effective dosage amounts in the blood of diltiazem in the morning when blood pressure begins to rise from the low levels reached during sleep, so as to be suitable as a chronotherapeutic preparation.

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It is a further object of this invention to provide a method of administration of the diltiazem preparations suitable as a chronotherapeutic so as to be effective in the morning at a time when the patient has most need of the diltiazem preparation. Further and other objects of the invention will be realized by those skilled in the art from the following summary of the invention and detailed description of embodiments thereof.

## SUMMARY OF THE INVENTION

According to one aspect of the invention, there is provided a controlled-release Galenical preparation (such as a tablet and a capsule) of pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a C<sub>max</sub> of Diltiazem in the blood at between about 10 hours and about 15 hours (preferably about 11–about 13 hours) after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and the preparation is adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII (at 100 rpm in 900 ml of water):

- (a) between about 1% and about 15% after about 2 hours, preferably between about 4% and about 8% after 2 hours;
- (b) between about 7% and about 35% after about 4 hours preferably between about 16% and about 21% after 4 hours;
- (c) between about 30% and about 58% after about 8 hours preferably between about 44% and about 52% after 8 hours;
- (d) between about 55% and about 80% after about 14 hours preferably between about 69% and about 76% after about 14 hours; and
- (e) in excess of about 75% after about 24 hours and preferably more than about 85% after 30 hours.

and/or (ii) into a buffered medium (such as, for example, phosphate buffer (U.S.P.)) having a pH between about 5.5 and about 6.5, preferably about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours, preferably between about 4% and about 15% after 2 hours;
- (b) between about 7% and about 45% after about 4 hours preferably between about 16% and about 30% after 4 hours;
- (c) between about 30% and about 68% after about 8 hours preferably between about 44% and about 62% after 8 hours;
- (d) in excess of about 75% after about 24 hours and preferably more than 80% after 24 hours.

Preferably no initial retard or delay is built into the preparation retarding/delaying release of Diltiazem from the preparation. Preferably the release rate from the preparation of the Diltiazem is less than about 15% of the total active per hour during dissolution. The preparation may be a diffusion controlled preparation such as, for example, a preparation

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incorporating the use of microgranules found, for example, in capsules and tablets; tablets; and coated tablets.

The preparation may comprise a plurality of microgranules or pellets, each microgranule comprising a central core or bead containing the form of diltiazem coated with a microporous membrane. The microgranules or pellets may be included in a capsule which dissolves when swallowed to release the microgranules or pellets. The preparation may also comprise a tablet in which the microgranules have been compressed to form the tablet. When compressed into tablet form, wax placebo beads (as known by persons skilled in the art) are preferably included to absorb the shock placed on the microgranules (core and membrane) during the tableting process. By doing so, the integrity of the microgranules containing the Diltiazem active remains intact and the release rate from the preparation is not affected. The tablet may also be coated or uncoated. The preparation may also comprise a sustained-release tablet coating from which preparation the Diltiazem is released. In this regard, the sustained release coating may be applied (sprayed onto) to each tablet.

Where the preparation comprises microgranules or pellets (for example) in the capsule or tablet (made, for example, by compressing the microgranules (with preferably wax placebo beads)), the central core may comprise Diltiazem or a pharmaceutically acceptable salt thereof associated with a wetting agent. The Diltiazem may be mixed (in whole or in part) with the wetting agent or may not be mixed with the wetting agent. The wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which each of the microgranules of the preparation will meet in the gastrointestinal tract.

If the Diltiazem and/or pharmaceutically acceptable salt is not mixed with the wetting agent then the microporous membrane should comprise with suitable adjuvants, a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer such as Eudragit NE30D (a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester) which hydrates the microgranule (including core). If the composition comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent, the microporous membrane is preferably the same. However, it may also comprise any suitable membrane which gives to the preparation the required dissolution characteristics.

In this regard, the preferred microporous membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose. This membrane will hydrate the core within the microporous membrane which, for example, may contain diltiazem surrounding a neutral pellet of sugar. The Eudragit NE30D in the membrane expands when it encounters gastrointestinal fluid to greater than 365% of its original size (elongation). This expandability of the membrane gives it the ability to hydrate the membrane and core. The mechanism of release is postulated to be that the membrane will swell while the fluids penetrate and hydrate the core and dissolve the diltiazem and wetting agent. This mechanism is, it is thought, driven by the concentration gradient through the membrane (high concentration inside and low concentration outside).

When Eudragit RS and Eudragit RL are combined to form the microporous membrane, the membrane can expand only very little before breakage or fracturing. The reason is that Eudragit RS expands minimally (about 6%) before the membrane material breaks or fractures changing its release



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mechanism from the core. Thus, the mechanism of release from this membrane is thought to be by "washing" the diltiazem through pores created when a plasticizer incorporated in the membrane is released in the gastrointestinal fluid. The diltiazem at the outer surface of the core would be washed from the core through the pores of the microporous membrane, then the diltiazem next presenting itself to the fluids after "washing" of the uppermost (outermost) diltiazem, and so on.

Instead of the wetting agent, any other suitable dissolution agent may be used to assist the release of the Diltiazem from the preparation. For example, instead of the preferred surface active (wetting) agent (surfactant), an organic acid (such as adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid and the like) may be incorporated in the core. In this regard, the presence of the organic acid in the core permits the diltiazem in the core to dissolve when the composition passes into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble. One of the membranes which may be used (though not preferred) is the combination of Eudragit RS and Eudragit RL disclosed in U.S. Pat. No. 4,721,619. (See column 1, lines 55-68 and column 2, lines 44-68.) The '619 patent also mentions the use of hydroxypropylmethylcellulose as a water-soluble membrane. The mechanism of release in this case is not by hydration of the core but rather by "washing" the Diltiazem through the pores created in the membrane (for example when the plasticizer in the membrane is released in the gastrointestinal fluid).

The Diltiazem may be present in the core in, for example, the hydrochloride salt form, in which event no dissolution agent may be required in the core.

Suitable preparations such as capsules of the microgranules making up the total Diltiazem active present, may comprise, in the core, Diltiazem hydrochloride between about 50% and about 85% (% w/w of the total preparation (for example, about 69% to about 73%)), a wetting agent (such as sucrose stearate) between about 2% and about 25% (% w/w of the total preparation) (for example about 7% to about 8%) together with suitable adjuvants in the core, and in the membrane between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose (for example about 0.3% to about 0.6%), and between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (such as Eudragit NB30D) (for example about 7% to about 11%).

The microgranules may also be compressed into tablets using suitable excipients. The percentages may be as described above. The tablets may be manufactured, as discussed above, using the microgranules with wax placebo beads and compressing the combination into tablets in the presence of, for example, hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide which have been blended with the microgranules and wax placebo beads before tableting. The tablets may then be coated or uncoated.

According to another aspect of the invention, there is provided a controlled-release Galenical preparation (such as a tablet and a capsule) of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, such as the hydrochloride salt, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg or more (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a C<sub>max</sub> of

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Diltiazem in the blood at between about 10 hours and about 15 hours (preferably about 11-about 13 hours) after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with food (such as a standardized FDA breakfast) and without food according to the same FDA guidelines or criteria.

The FDA guidelines are those entitled:

"GUIDANCE ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS IN VIVO BIOEQUIVALENCE AND IN VITRO DISSOLUTION TESTING" prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993 which is incorporated herein by reference; and

"GUIDANCE STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER DESIGN" prepared under 21 CFR 10.90(b)(9) by Mei-Ling Chen, Ph.D., Division of Bioequivalence Review Branch II dated Jun. 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated Jun. 26, 1992, approved by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence dated Jun. 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated Jun. 29, 1992 which is incorporated herein by reference.

In small part the said "GUIDANCE" documents provide as follows:

Pharmacokinetic Analysis of Data: Calculation of area under the plasma concentration-time curve to the last quantifiable concentration (AUC<sub>0-∞</sub>) and to infinity (AUC<sub>0-∞</sub>), C<sub>max</sub> and T<sub>max</sub> should be performed according to standard techniques.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C<sub>max</sub> data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. See also Division of Bioequivalence Guidance Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.

Statistical Analysis of Pharmacokinetic Data: The log transformed AUC and C<sub>max</sub> data should be analyzed statistically using analysis of variance. These two parameters for the test product should be shown to be within 80-125% of the reference product using the 90% confidence interval. Fluctuation for the test product should be evaluated for comparability with that for the reference product. For further information on statistical analysis, see the Division of Bioequivalence Guidance Statistical procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.

## 2. Multiple Dose Studies

At a minimum, the following pharmacokinetic parameters for the substance(s) of interest should be measured in a multiple dose bioequivalence study:

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- a. Area under the plasma/blood concentration—time curve from time zero to time  $\tau$  over a dosing interval at steady state ( $AUC_{0-\tau}$ ), where  $\tau$  is the dosing interval.
  - b. Peak drug concentration ( $C_{max}$ ) and the time to peak drug concentration ( $T_{max}$ ), obtained directly from the data without interpolation, after the last dose is administered.
  - c. Drug concentrations at the end of each dosing interval during steady state ( $C_{min}$ ).
  - d. Average drug concentration at steady state ( $C_{av}$ ), where  $C_{av} = AUC_{0-\tau} / \tau$ .
  - e. Degree of fluctuation (CF) at steady state, where  $DF = 100\% \times (C_{max} - C_{min}) / C_{av}$ .
- Evidence of attainment of steady state for the test and reference products should be submitted in the bioequivalence study report.

#### B. Statistical Analysis

Parametric (normal-theory) general linear model procedures are recommended for the analysis of pharmacokinetic data derived from in vivo bioequivalence studies. An analysis of variance (ANOVA) should be performed on the pharmacokinetic parameters AUC and  $C_{max}$  using General Linear Models (GLM) procedures of SAS (4) or an equivalent program. Appropriate statistical models pertaining to the design of the bioequivalence study should be employed. For example, for a conventional two-treatment, two-period, two-sequence (2x2) randomized crossover study design, the statistical model often includes factors accounting for the following sources of variation:

1. Sequence (sometimes called Group or Order)
2. Subjects, nested in sequences
3. Period (or Phase)
4. Treatment (sometimes called Drug or Formulation)

The sequence effect should be tested using the [subject (sequence)] mean square from the ANOVA as an error term. All other main effects should be tested against the residual error (error mean square) from the ANOVA. The LSMEANS statement should be used to calculate least squares means for treatments. The ESTIMATE statement in SAS should be used to obtain estimates for the adjusted differences between treatment means and the standard error associated with these differences.

The two one-sided hypotheses at the  $\alpha=0.05$  level of significance should be tested for AUC and  $C_{max}$  by constructing the 90% confidence interval for the ratio between the test and reference averages.

#### III. Logarithmic Transformation of Pharmacokinetic Data

##### A. Statistical Assumptions

The assumptions underlying the ANOVA are (5):

1. Randomization of samples
2. Homogeneity of variances
3. Additivity (linearity) of the statistical model
4. Independency and normality of residuals

In bioequivalence studies, these assumptions can be interpreted as follows:

1. The subjects chosen for the study should be randomly assigned to the sequences of the study.
2. The variances associated with the two treatments, as well as between the sequence groups, should be equal or at least comparable.
3. The main effects of the statistical model, such as subject, sequence, period and treatment effect for

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a standard 2x2 crossover study, should be additive. There should be no interactions between these effects.

4. The residuals of the model should be independently and normally distributed. In other words, data from bioequivalence studies should have a normal distribution.

If these assumptions are not met, additional steps should be taken prior to the ANOVA including data transformation to improve the fit of the assumptions or use of a nonparametric statistical test in place of ANOVA. However, the normality and constant variance assumptions in the ANOVA model are known to be relatively robust, i.e., small or moderate departure from each (or both) of these assumptions will not have a significant effect on the final result.

#### B. Rationale for Log Transformation

##### 1. Clinical Rationale

In a meeting in September 1991, the Generic Drugs Advisory Committee (GDAC) concluded that the primary comparison of interest in a bioequivalence study was the ratio rather than the difference between average parameter data from the test and reference formulations. Using log transformation, the general linear statistical model employed in the analysis of bioequivalence data allows inferences about the difference between the two means on the log scale, which can then be retransformed into inferences about the ratio of the two averages (means or medians) on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than the difference (6).

##### 2. Pharmacokinetic Rationale

Westlake (7,8) observed that a multiplicative model is postulated for pharmacokinetic parameters in bioavailability/bioequivalence studies, i.e., AUC and  $C_{max}$  (but not  $T_{max}$ ). Assuming that elimination of the drug is first order and only occurs from the central compartment, the following equation holds after an extravascular route of administration:

$$AUC_{0-\infty} = FD/CL \\ = FD/(VK_e)$$

where F is the fraction absorbed, D is the administered dose, and FD is the amount of drug absorbed. CL is the clearance of a given subject which is the product of the apparent volume of distribution (V) and the elimination rate constant ( $K_e$ ).<sup>2</sup>

<sup>2</sup>Note that a more general equation can be written for any multi-compartmental model as  $AUC_{0-\infty} = FD/(V_{ss}\lambda_z)$  where  $V_{ss}$  is the volume of distribution relating drug concentration in plasma or blood to the amount of drug in the body during the terminal exponential phase, and  $\lambda_z$  is the terminal slope of the concentration-time curve.

The use of AUC as a measure of the amount of drug absorbed thus involves a multiplicative term (CL) which might be regarded as a function of the subject. For this reason, Westlake contends that the subject effect is not additive if the data is analyzed on the original scale of measurement.

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Logarithmic transformation of the AUC data will bring the CL ( $VK_d$ ) term into the equation in an additive fashion.

$$\ln AUC_{0-\infty} = \ln F + \ln D - \ln V - \ln K_1$$

Similar arguments were given for  $C_{max}$ . The following equation applies for a drug exhibiting one compartmental characteristics:

$$C_{max} = (FD/V) \times e^{-K_e t_{max}}$$

where again F, D and V are introduced into the model in a multiplicative manner. However, after logarithmic transformation, the equation becomes

$$\ln C_{max} = \ln F + \ln D - \ln V - K_e t_{max}$$

Log transformation of the  $C_{max}$  data also results in the additive treatment of the V term.

### 3. Statistical Rationale

Logarithmic transformation of the data from bioequivalence studies can be used to circumvent the use of estimates of the reference product average for computation of the confidence interval for the ratio of product averages. This is an advantage for the cases where a least squares estimate for the reference product mean is not well defined. Standard parametric methods are ill-suited to making inferences about the ratio of two averages, though some valid methods do exist (9). Log transformation changes the problem to one of making inferences about the difference (on the log scale) of two averages, for which the standard methods are well suited.

Many biological data correspond more closely to a log-normal distribution than to a normal distribution. The plasma concentration data including the derived parameters AUC and  $C_{max}$  tend to be skewed, and their variances tend to increase with the means. Log transformation is likely to remedy this situation and make the variances independent of the mean. In addition, frequency distributions skewed to the left (with a long tail to the right) are often made more symmetrical by log transformation.

This argument is actually less persuasive than the argument based on the additivity of the statistical model because it is based largely on the between-subject distribution of AUC and  $C_{max}$  values. For crossover studies, it is largely the within-subject distribution of values that determines the validity and efficiency of the standard parametric methods of analysis.

Despite the arguments regarding the effect of log transformation on normality of bioequivalence data, the division of Bioequivalence recognizes that the limited sample size (20-30 subjects) in a bioequivalence study precludes a reliable determination of the underlying normal distribution of the data set either with or without log transformation.

### C. General Procedures

Based on the arguments in the preceding section, the Division of Bioequivalence recommends that the pharmacokinetic parameters AUC and  $C_{max}$  be log transformed. Firms are not encouraged to test for normality of data distribution after log transformation, nor should they employ normality of data

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distribution as a justification for carrying out the statistical analysis on the original scale.

Robustness of a balanced study to nonnormality of the data plus use of log transformation will be adequate in most cases.

If a firm believes that the data of a particular bioequivalence study should be statistically analyzed on the original scale rather than the log scale, justification based upon a sound scientific rationale, as well as the statistical methods to be used, ought to be submitted to and reviewed by the Division of Bioequivalence.

Thus according to another aspect of the invention, the results of biostudies employing a formulation according to an embodiment of the invention, clearly show that when given at different times (P.M. or A.M. dosing) and under different conditions (with and without food) though they achieve their maximum bioavailability at the same  $T_{max}$  when the formulation is given at night (no food) a higher bioavailability (for example a significantly higher bioavailability exceeding 25% ( $C_{max}$ ) is attained than when given in the morning without food (according to FDA guidelines) and bioequivalence when given with food or without food in the morning according to the FDA guidelines.

According to another aspect of the invention, a method of treatment of a patient's hypertension and/or angina is provided comprising administration of a preparation of Diltiazem described above, to the patient in the evening for example at about 7:00-about 11:00 p.m. for effective treatment of the patient's hypertension and/or angina the next morning, for example between about 6:00 a.m. and about noon.

According to another embodiment of the invention a method of treatment of a patient's hypertension and/or angina is provided comprising administration of a preparation which exhibits a higher bioavailability (exceeding, for example, 25%) when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food (for example given a standardized FDA breakfast) and without food according to the same FDA guidelines or criteria.

Thus a 24-hour diltiazem preparation is provided wherein the  $C_{max}$  of diltiazem in the blood is provided from about 10-15 hours after administration of a single dosage to a patient or about 9-15 hours after multiple dosages over a number of days and displays the dissolution pattern described above determined according to USP 23, page 1791 using Apparatus 1. Apparatus 1 is described as consisting of the following:

a covered vessel made of glass or other inert, transparent material<sup>1</sup>; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at  $37 \pm 0.5^\circ$  during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.<sup>2</sup> The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of



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the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within +4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in FIG. 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5  $\mu$ m) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 $\pm$ 2 mm during the test.

<sup>1</sup> The materials should not sorb, react, or interfere with the specimen being tested.

<sup>2</sup> If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

(taken from USP 23)

According to another aspect of the invention, where the preparations comprise cores wherein the diltiazem is in association with a wetting agent, the wetting agent may be selected from:

sugars;  
saccharose, mannitol, sorbitol;  
lecithins;

C<sub>12</sub> to C<sub>20</sub> fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.) such as sucrose stearate marketed under the trade name of Crodesta;

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Bumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France)

Metal salts such as NaCl or sodium lauryl sulphate

The microporous membrane may be of any suitable material or combination of materials known in the art. Where the wetting agent is in association with the diltiazem in the core and not mixed therewith, the microporous membrane should comprise a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer such as a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester such as Eudragit NE30D. This enables the bead to be hydrated by the introduction of intestinal fluids into the bead hydrating the bead and therefore mixing the diltiazem and the wetting agent. The membrane itself, because of the fluids passing through the membrane, will swell. This membrane acts differently from membranes which do not swell. These other non-hydratable or swellable membranes may be made-up, for example, of water-soluble or water-dispersible polymers or copolymers and a water-, acid- and base-insoluble polymer such as Eudragit RS which swell less easily (owing to the reduced content in quaternary ammonium groups) and are only slightly permeable to active ingredients. This membrane is best suited for coating cores of Diltiazem mixed with a wetting agent or organic acid.

Among materials which may be used to make the microporous membranes, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, ethyl celluloses such as Ethocels from Dow U.S.A. and Aquacoat of FMC U.S.A., hydroxypropylmethylcellulose, hydroxyethylcellulose and hydroxypropylcellulose.

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Additionally, adjuvants may be put in the formulation as required such as plastifying agents (plasticizer), pigments, fillers, lubricants and anti-foaming agents. For example talc and/or magnesium stearate may be used as a lubricant, dibutyl sebecate as plasticizer, titanium dioxide as a pigment, Tween 80 as an emulsifier and silicone oil as an anti-foaming agent.

The amount of the microporous membrane is adjusted to provide the sustained release characteristics described.

Thus embodiments of the invention have higher bioavailability (greater AUC and C<sub>max</sub> at the same time (T)) when given at night than given in the morning without food according to the FDA guidelines discussed previously and are bioequivalent when given in the morning with food to formulation given in the morning without food according to the FDA guidance.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be illustrated with reference to the following examples and with reference to the following Figures:

FIG. 1: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood after a specified period after a single dose of a 300 mg Diltiazem capsule preparation made according to an embodiment of the invention.

FIG. 2: is a graph illustrating the Diltiazem Concentration (ng/mL) in the blood over a 24-hour period after giving multiple doses of the same 300 mg Diltiazem capsules referred to with respect to FIG. 1 but over a number of days.

FIG. 3: is a graph illustrating dissolution profiles generated according to USP 23 using Apparatus 1 (baskets) at 100 r.p.m. in 900 ml of water for capsule preparations made according to embodiments of the invention (120 mg, 180 mg, 240 mg and 300 mg of Diltiazem active).

FIG. 4: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in water according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 5: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in gastric fluid according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 6: illustrates the dissolution profile of a 120 mg capsule preparation of Diltiazem HCl in intestinal fluid according to USP 23 (Apparatus 1-baskets) according to an embodiment of the invention.

FIG. 7: is a graphic comparison of the blood level concentrations of a preparation (240 mg) made according to an embodiment of the invention and Dilacor (240 mg), a 24-hour oral sustained release dosage form of Diltiazem.

FIG. 8: is a graphic comparison of the blood level concentrations of a preparation (240 mg) made according to an embodiment of the invention and Tiazac (240 mg), a 24-hour oral sustained-release dosage form of Diltiazem.

FIG. 9: illustrates graphically the Mean Diltiazem Concentration when administration of the same dosage form, is given in the P.M., in the A.M. with food and in the A.M. with fasting (without food) by 29 persons.

FIG. 10: illustrates graphically the Mean Diltiazem Concentration when the dosage form is an open capsule sprinkled on applesauce and swallowed and the dosage form is swallowed intact by 30 persons.

Preparations were manufactured according to the percentages and constituents set out below:

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Component	% W/W
(1) Diltiazem hydrochloride	69-73
(2) Microcrystalline cellulose (Avicel ph101)	8-9.5
(3) Povidone K30	1-2
(4) Sucrose stearate (crodesta F150)	7-8
(5) Magnesium stearate NF	0.5-2.5
(6) Talc USP	0.5-5.0
(7) Titanium dioxide (USP)	0.15-0.3
(8) Hydroxypropylmethylcellulose 2910	0.3-0.6
(9) Polysorbate 80 (tween)	0.01-0.025
(10) Simeticone C emulsion USP (dry of 30%)	0.01-0.015
(11) Budragit NE30 D (dry of 30%)	7-11
(12) Purified water USP	0

Two Examples of preparations given the above percentages were made as 120 mg and 180 mg strengths of Diltiazem (as the HCl salt) in capsule form.

## Example 2

Strength	120 mg capsule
(1)	120.00
(2)	13.63-16.18
(3)	1.7-3.41
(4)	11.92-13.63
(5)	0.852-4.26
(6)	0.852-8.52
(7)	0.256-0.511
(8)	0.511-1.02
(9)	0.0170-0.0426
(10)	0.017-0.0256
(11)	11.92-18.74
(12)	0

## Example 3

Strength	180 mg capsule
(1)	180.00
(2)	20.44-24.27
(3)	2.56-5.11
(4)	17.88-20.44
(5)	1.278-6.388
(6)	1.278-12.78
(7)	0.383-0.767
(8)	0.7665-1.533
(9)	0.0256-0.0639
(10)	0.0255-0.383
(11)	17.886-28.106
(12)	0

240 mg, 300 mg, 360 mg and 420 mg strength preparations in capsule form of Diltiazem (as the HCl salt) were also prepared having the same percentages. They provide the release patterns shown in FIG. 3. The dissolution profiles of all of the strengths were generated from biobatches of capsules using Apparatus 1 (baskets) at 100 RPM in 900 ml of water in accordance with USP 23.

Less than 20% of the formulation is dissolved after about four hours (for example between about 16%-21%) with less than about 10% dissolved in the first two hours (for example between about 4%-about 8%). Less than about 50% is

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released after 8 hours (for example between about 44%-52%). Less than about 73% is released after 14 hours (for example 69%-76%). Preferably in excess of about 85% is released after 24 hours.

Specifically, samples of 120 mg capsules of Diltiazem HCl (made according to the embodiment of the invention) had the following dissolution profile:

Percent Dissolved - Time Elapsed									
	2 h (%)	4 h (%)	8 h (%)	14 h (%)	24 h (%)				
5	8	19	19	49	49	72	72	88	88
4	5	16	14	32	44	76	69	93	85
5	6	18	16	50	49	72	73	88	90
7	6	21	17	54	48	76	72	92	87
5	8	17	19	51	50	74	74	92	91
6	7	18	19	52	52	74	75	90	92
Mean (%)	6	18	50	73	90				
RSD	21.3	10.5	5.1	2.7	2.6				

Samples of 180 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

Percent Dissolved - Time Elapsed									
Lapsed Time	2 h (%)	4 h (%)	8 h (%)	14 h (%)	24 h (%)				
30	8	7	21	20	52	52	76	73	91
	6	7	19	20	52	51	76	73	93
	5	6	16	18	48	50	72	72	89
	6	7	19	18	52	49	76	72	98
	7	7	20	19	51	51	73	74	91
35	8	7	20	21	51	51	74	73	92
Mean (%)	7	19	51	74	91				
RSD	12.8	7.4	2.5	2.1	1.7				

Samples of 240 mg capsules of Diltiazem HCl (made according to an embodiment of the invention) had the following dissolution profiles:

Percent Dissolved - Time Elapsed									
	2 h (%)	4 h (%)	8 h (%)	14 h (%)	24 h (%)				
45	6	4	19	16	46	48	73	71	86
	6	5	18	15	48	45	70	68	85
	5	5	18	17	49	49	71	72	86
50	4	7	16	18	46	48	68	71	83
	6	4	18	15	49	50	70	68	84
	6	6	18	17	48	48	70	71	85
Mean (%)	5	17	48	70	85				
RSD	18.5	7.7	2.9	2.3	1.7				

Samples of Diltiazem HCl capsules 300 mg (made according to an embodiment of the invention) had the following dissolution profile:

Percent Dissolved - Time Elapsed									
	2 h (%)	4 h (%)	8 h (%)	14 h (%)	24 h (%)				
60	3	4	16	16	46	45	68	67	83
	6	5	17	16	49	45	73	67	90
	6	5	16	16	46	46	69	68	84

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Percent Dissolved - Time Elapsed									
	2 h (%)	4 h (%)	8 h (%)	14 h (%)	24 h (%)				
	5	5	16	16	46	46	69	69	83
	6	4	17	15	46	45	68	68	82
	5	5	17	17	46	47	69	70	84
Mean (%)	5	16	46	69	85				
RSD	13.2	3.8	2.4	2.3	2.8				

Additionally, the following Dissolution Profiles were obtained for the samples of 120 mg Diltiazem HCl Capsules:

Medium: Water			
Diltiazem HCl Capsules			
Hour	% Dissolved (Average of 12 capsules)	Range [%]	RSD
2	6	4-8	17.6
4	18	14-21	9.8
8	50	44-54	5.1
14	73	69-76	2.8
24	90	86-93	2.5

Medium: Gastric Fluid			
Diltiazem HCl Capsules			
Hour	% Dissolved (Average of 12 capsules)	Range [%]	RSD
2	5	3-6	18.8
4	16	14-18	9.0
8	49	47-52	3.5
14	73	71-75	1.8
24	87	85-89	1.5

Medium: Intestinal Fluid			
Diltiazem HCl Capsules			
Hour	% Dissolved (Average of 12 capsules)	Range [%]	RSD
2	5	3-7	26.0
4	17	14-20	12.0
8	43	40-47	6.1
14	64	53-69	8.1
24	78	65-85	8.1

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Other Dissolution Profiles were determined of embodiments of the invention

Medium—USP Water

Apparatus: USP #1 (baskets) at 100 rpm

Diltiazem 120 mg Capsules					
TIME [h]	2	4	8	14	24
vessel 1	5%	19	49	72	88
vessel 2	4	16	52	76	93
vessel 3	5	18	50	72	88
vessel 4	7	21	54	76	92
vessel 5	5	17	51	74	92
vessel 6	6	18	52	74	90
vessel 7	8	19	49	72	88
vessel 8		14	44	69	86
vessel 9		16	49	73	90
vessel 10	6	17	48	72	87
vessel 11	8	19	50	74	91
vessel 12	7	19	52	75	92
MEAN	6%	18	50	73	90
SD	1.3	1.9	2.6	2.0	2.3
RSD	21.3	10.5	5.1	2.7	2.6
RANGE	4-8	14-21	44-54	69-76	86-93

Medium—Gastric

Apparatus: USP #1 (baskets) at 100 rpm

Diltiazem 120 mg Capsules					
TIME [h]	2	4	8	14	24
vessel 1	3	14	51	74	88
vessel 2	6	17	48	72	85
vessel 3	5	17	49	72	85
vessel 4	5	15	48	72	87
vessel 5	4		47	71	86
vessel 6	6	18	50	72	86
vessel 7		15	49	73	88
vessel 8	4	14	48	71	86
vessel 9	5	17	51	74	88
vessel 10	6	18	52	74	88
vessel 11	6	18	50	75	89
vessel 12	5	17	50	73	87
MEAN	5	16	49	73	87
SD	0.9	1.5	1.7	1.3	1.3
RSD	19.0	9.0	3.5	1.8	1.5
RANGE	3-6	14-18	47-52	71-75	85-89

Medium—Intestinal

Apparatus: USP #1 (baskets) at 100 rpm

Diltiazem 120 mg Capsules					
TIME [h]	2	4	8	14	24
vessel 1	7	19	45	67	81
vessel 2	4	14	40	64	79
vessel 3	7	20	47	69	83
vessel 4	5	19	46	68	83
vessel 5		17	41	58	69
vessel 6		17	45	69	83
vessel 7	4	17	40	53	65

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-continued

Diltiazem 120 mg Capsules					
TIME [h]	2	4	8	14	24
vessel 8	5	17	42	65	78
vessel 9	5			58	73
vessel 10	5	17	47	68	85
vessel 11	4	15	44	64	81
vessel 12	4	15	43	64	81
MEAN	5	17	43	64	78
SD	1.2	2.0	2.7	5.2	6.4
RSD	25.9	13.0	6.1	8.1	8.1
RANGE	3-7	14-20	40-47	53-69	65-85

Briefly, the dosages in Examples 1 (120 mg) and 2 (180 mg), the 240 mg, 300 mg, 360 mg and 420 mg dosages were manufactured by mixing the core (bead) ingredients (diltiazem, microcrystalline cellulose, povidone, sucrose stearate) by introducing the components into a planetary mixer and granulating same and mixing with purified water. The plastic mass was then extruded to provide an extrudate. The extrudate was subsequently spheronized to produce diltiazem spheres in admixture with the wetting agent. The spheres (cores) were dried in an oven and sieved to the appropriate size cores or beads.

The membrane was prepared by mixing the hydroxypropylmethylcellulose, titanium dioxide, talc, magnesium stearate, Polysorbate 80 and Simethicone C emulsion and thereafter combined with the Eudragit NE30D and water. The spheronized cores were coated with the appropriate thickness of membrane by spraying the cores, coating same. Thus the cores (beads) were coated with the coating suspension to produce the microgranules or pellets. The microgranules or pellets were then dried.

In more detail the process combines Diltiazem Hydrochloride USP, Microcrystalline cellulose NF (Avicel PH 101), Povidone K30 USP and Sucrose Stearate (Crodesta F160) as follows:

The following were screened through a 1.9 mm screen and added to a mixer bowl:

Diltiazem  
Avicel PH 101  
Povidone K30.

To remove large agglomerates, the Crodesta 7.98 kg was screened through a 1.0-1.2 mm screen and added to the same mixing bowl. The items were then blended in an AMF blender at 50 RPM. 1 kg of the above dry blend was set aside to be used as dusting powder (Diltiazem Dusting Powder). The remainder of the blend was continued to be blended at 50 rpm until adequately granulated. The granulated material was then loaded into the hopper of an extruder (such as EXDCS100 or EXDS 60). The granulation was extruded and without breaking up the extrudate, the extrudate was collected. The extrudate was then spheronized into the cores (beads) of the desired size and were dusted as desired by the Diltiazem Dusting Powder set aside. The beads were then dried by spreading them on trays and drying in an oven set at about 57° C. The Drying Temp. was in the order of 55-60° C. for about 12 hours (in the order of 12-16 hours). The dried cores (beads) were sieved to collect those of appropriate size (0.7-1.4 mm).

A Eudragit NE30D and hydroxypropylmethylcellulose coating suspension, was made. The following:

Magnesium Stearate NF  
Talc USP  
Titanium Dioxide USP

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Hydroxypropylmethylcellulose 2910 USP (Pharmacoat 606)

Polysorbate 80 NF (Tween 80)

Simethicone C Emulsion USP

and pure water were combined within a Silverson Mixer. Water was first mixed with Polysorbate 80 and the Simethicone. The HPMC was then added, then titanium dioxide, then talc and then the Magnesium Stearate. The mixture was stored for 2 hours. The Eudragit NE30D was screened through a 0.310 mm sieve and added to the mixture.

The beads were then coated with the suspension by using an Aerocoater™ and spraying the beads (which have been preheated to 26° C.) with the coating suspension to achieve the desired thickness (about 0.05 mm). The beads were then dried by spreading on trays and drying at 40-45° C. for 10-12 hours.

Diltiazem HCl 300 mg capsules made according to an embodiment of the invention were tested in a single dose study to determine their bioavailability, their C<sub>max</sub> and T<sub>max</sub>, their rate and extent of absorption. Blood sampling for drug content analysis was carried out at 0.0 (predrug) 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 42 and 48 hours post-drug. Vital sign and 12-Lead ECG monitoring were conducted at 0 (predrug) 2, 6, 8 and 12 hours post-drug. The following was determined from the plasma study:

Mean Pharmacokinetic Parameters for Plasma Diltiazem  
(n = 41)

Parameter	1 × 300 mg Mean (% CV)
AUC (0-t)(ng.hr/mL)	2703.83 (36.26)
AUG (0-inf)(ng.hr/mL)	2786.95 (36.39)
C <sub>max</sub> (ng/mL)	146.33 (38.43)
T <sub>max</sub> (hours)	13.17 (14.79)
t <sub>1/2</sub> (hours)	6.96 (17.56)
K <sub>el</sub> (hour <sup>-1</sup> )	0.102 (15.983)

Mean Plasma Diltiazem Concentrations (ng/mL)  
(n = 41)

SAMPLE TIME (HOURS)	1 × 300 mg
0.00	0.00 ± 0.00
1.00	0.76 ± 2.20
2.00	4.92 ± 3.87
3.00	10.97 ± 5.92
4.00	20.01 ± 10.77
5.00	33.46 ± 18.39
6.00	70.21 ± 37.03
8.00	95.43 ± 41.50
10.00	110.16 ± 47.43
12.00	132.84 ± 52.04
14.00	139.54 ± 55.11
16.00	126.35 ± 50.23
18.00	105.74 ± 40.86
24.00	62.84 ± 24.20
30.00	43.92 ± 16.94
36.00	25.67 ± 11.46
42.00	13.40 ± 7.37
48.00	7.50 ± 4.46

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Mean Pharmacokinetic Parameters for Plasma Diltiazem (n = 35)	
Parameter	Geometric Mean Arithmetic Mean (C.V.) 1 x 300 mg
AUC (0-1 hours)(ng.hr/mL)	2682.87 2872.06 (38.44)
AUC (0-x)(ng.hr/mL)	1955.92 2075.00 (35.63)
AUC (0-infinity)(ng.hr/mL)	2847.57 3055.19 (39.05)
C <sub>max</sub> (ng/mL)	134.96 144.00 (37.17)
T <sub>max</sub> (hours)**	13.00 (2.92)
t <sub>1/2</sub> (hours)*	8.69 (22.85)
K <sub>el</sub> (hour <sup>-1</sup> )*	0.084 (22.860)

\*These are arithmetic means (CV %).

\*\*This is median (±S.D.).

With reference to FIGS. 1 and 2, it is clear the 300 mg capsule preparation made according to an embodiment of the invention provides the appropriate Diltiazem blood levels at the appropriate time to be suitable for administration as a chronotherapeutic—being given in the evening to provide effective concentrations of Diltiazem the following morning. This suitability is illustrated with reference to FIGS. 7 and 8. In FIG. 7, the 240 mg Diltiazem preparation made according to the embodiment of the invention provides elevated blood levels that are effective all morning for effective treatment of the patient with Diltiazem. However, the Dilacor formulation (given either in the evening or the following morning) does not protect the patient from 6:00 a.m.–noon, the more dangerous period.

The same is true with FIG. 8. Tiazac given in the morning, does not provide the protection. Further, peak plasma concentrations for Tiazac are achieved after about 7 hours after dose administration.

A 3-way single-dose study was undertaken using the same formulation (420 mg capsule) administered in the P.M. (10:00 P.M.) without food, and in the A.M. dosing with and without food.

### 3-Way Single-Dose Study

A: Formulation According to Embodiment of Invention—Fasting (AM Dosing)

B: Formulation According to Embodiment of Invention—Fed (AM Dosing)

C: Formulation According to Embodiment of Invention—(PM Dosing)

N=29

The results illustrated in FIG. 9A and FIG. 9B were found whose mean were graphically illustrated in FIG. 9.

A 2-way single-dose fasting study was undertaken using the same formulation (420 mg capsule) administered in the following manners—capsule intact and capsule opened and sprinkled on applesauce and ingested.

### 2-Way Single Dose Fasting Study

A: Formulation According to Embodiment of Invention—Open Capsule Sprinkled on Applesauce

B: Formulation According to Embodiment of Invention—Capsule Intact

N=30 (FINAL DATA)

The results illustrated in FIGS. 10A, 10B and 10C were found whose mean were graphically illustrated in FIG. 10.

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The preparations according to embodiments may also be made as tablets. The tablets may be made as compressed tablets in the desired strengths (for example 120 mg–540 mg or more Diltiazem) incorporating the microgranules. The tablets may even be scored to permit division into smaller doses.

Tablets may be made as follows using the microgranules or pellets, wax placebo beads and hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide as follows:

The microgranules of Diltiazem may be the following:

Magnesium Stearate  
Talc  
Titanium Dioxide  
Hydroxypropylmethyl-Cellulose 2910  
Polysorbate 80  
Simethicone Emulsion  
Eudragit NE30D  
Diltiazem Hydrochloride  
Microcrystalline Cellulose

Povidone K30

Sucrose Stearate

Purified Water

The wax placebo beads may be the following:

Microcrystalline Wax NF  
Pregelatinized Starch  
Sodium Starch Glycolate  
Titanium Dioxide  
Carbon Dioxide

The microgranules, wax placebo beads, hydrogenated vegetable oil, sodium starch glycolate and silicone dioxide may be combined and compressed into the desired strengths of tablets, for example 240 mg, 300 mg and 360 mg tablets. Briefly, to form the microgranules, Diltiazem HCl, Microcrystalline Cellulose, Povidone 30, Sucrose Stearate may be mixed to form a "dry blend". A 1 kg portion of the dry blend may be removed and stored in a separate labeled container as the Dusting Powder, for use in subsequent manufacturing steps (if desired). Following the removal of the Dusting Powder, Purified Water is added to the dry blend and mixed to create a plastic mass. The plastic mass is extruded through a 1.0 mm screen to form a spaghetti like extrudate. This extrudate is then spheronized into beads. During the spheronization process Dusting Powder is added to dry the beads and provide them with a smooth aspect (if required). The addition of Dusting Powder also prevents the newly spheronized beads from sticking together. The spheronized beads are tray dried for 12–16 hours and sieved to select beads that are larger than 0.7 mm and smaller than 1.4 mm in diameter.

The beads are loaded into a preheated (40–45° C.) fluid bed Aerocoater. Coating suspension is applied at an amount of 10% by spray coating. The resulting Diltiazem Microgranules (coated beads) are dried for between 10–12 hours and the dried coated beads are sieved to select coated beads that are larger than 0.7 mm and smaller than 1.7 mm in diameter.

For the manufacture of the placebo wax beads, Microcrystalline Wax, Pregelatinized Maize Starch, Sodium Starch Glycolate and Titanium Dioxide are mixed in a high shear mixer and heated to 64° C. (jacket temperature 70° C.). The resulting melt is cooled by the addition of liquid CO<sub>2</sub> to form the solid starters of the pellets. The pellet starters are mixed and the size is increased by the gradual turning of the impeller for a fixed timeperiod (mixing time is directly related to the impeller speed and the time to reach a temperature of 57±2° C.). The resulting beads are sieved to select beads larger than 0.7 mm and smaller than 1.4 mm in diameter.



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For manufacturing the Diltiazem chronotherapeutic tablets, the placebo wax beads and the microgranules of Diltiazem are blended at a ratio of about 2:3 (placebo wax beads: microgranules of Diltiazem) with Hydrogenated Vegetable Oil (lubricant), Sodium Starch Glycolate (disintegrant) and Silicone Dioxide (lubricant) added. The blend is tableted under low pressure (approximately 6-8 Sc) to form the compressed Diltiazem Tablets.

In the compressed tablets, the placebo wax beads serve to absorb the shock placed on the microgranules of Diltiazem during the tableting process. By doing so the integrity of the microgranules remains in tact and the release rate of the diltiazem is not affected.

As many changes can be made to the embodiments of the invention without departing from the scope thereof, it is intended that all material contained herein be determined as illustrative of the invention and not in a limiting sense.

The invention claimed is:

1. An orally administrable controlled-release composition comprising a pharmaceutically acceptable form of diltiazem selected from the group consisting of diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours, the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of diltiazem, the diltiazem in the core of each bead associated with excipients, the at least one coating covering the core comprising an amount of a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating comprising the following constituents:

- (i) an amount of at least one hydrophilic polymer which is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose, and/or an amount of at least one lubricant which is selected from the group consisting of talc, and magnesium stearate; and
- (ii) an amount at least one water-, acid- or base-insoluble neutral acrylic polymer, wherein said constituents (i) and (ii) which comprise said coating, the ratios thereof, and the amount of said coating are formulated such that said orally administrable composition:
  - A) in vitro exhibits the following in vitro release characteristics;
    - (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
      - (a) between about 1% and about 15% after about 2 hours;
      - (b) between about 7% and about 35% after about 4 hours;
      - (c) between about 30% and about 58% after about 8 hours;
      - (d) between about 55% and about 80% after about 14 hours;
      - (e) in excess of about 75% after about 24 hours; and/or
    - (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:

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- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours; and further wherein said orally administrable composition having said in vitro release characteristics results in a composition that:
  - B) when orally given to humans exhibit the following properties:
    - (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and
    - (ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria; and
    - (iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration.

2. The controlled release preparation of claim 1 wherein said neutral acrylic polymer is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester.

3. The controlled-release preparation of claim 1 in which the form of diltiazem is adapted to be control released after administration of the preparation over a period of time and is more preferably adapted to release the diltiazem

- (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
  - (a) between about 4% and about 8% after about 2 hours;
  - (b) between about 16% and about 21% after about 4 hours;
  - (c) between about 44% and about 52% after about 8 hours;
  - (d) between about 69% and about 76% after about 14 hours; and
  - (e) and in excess of about 85% after about 24 hours; and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium:
    - (a) between about 4% and about 15% after about 2 hours;
    - (b) between about 16% and about 30% after about 4 hours;
    - (c) between about 44% and about 62% after about 8 hours;
    - (d) in excess of about 80% after about 24 hours.

4. The preparation of claim 1 wherein the Cmax of diltiazem in the blood is obtained between about 11-about 13 hours after administration of the preparation.

5. The preparation of claim 1, 2, 3 or 4 wherein the form of diltiazem is Diltiazem HCl.

6. The preparation of claim 4 wherein the preparation is a diffusion controlled preparation.

7. The preparation of claim 3 wherein the preparation releases the diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

8. The preparation of claim 7 in capsule form.

9. The preparation of claim 7 in tablet form.

10. The preparation of claim 7 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core

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comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

11. The preparation of claim 10 wherein the diltiazem is mixed (in whole or in part) with the wetting agent.

12. The preparation of claim 11 wherein the wetting agent assists to maintain the solubility of the diltiazem in each microgranule, ensuring that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

13. The preparation of claim 12 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

14. The preparation of claim 10 wherein the preparation comprises a mixture of the diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

15. The preparation of claim 14 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

16. The preparation of claim 15 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

17. The preparation of claim 11 wherein the diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

18. The preparation of claim 7 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the diltiazem from the preparation.

19. The preparation of claim 18 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

20. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 1 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the method comprising administering to a patient in need thereof the preparation in the evening.

21. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 3 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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ration of diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

39. The preparation of claim 1 wherein the preparation contains 120 mg of diltiazem.

40. The preparation of claim 1 wherein the preparation contains 180 mg of diltiazem.

41. The preparation of claim 1 wherein the preparation contains 240 mg of diltiazem.

42. The preparation of claim 1 wherein the preparation contains 300 mg of diltiazem.

43. The preparation of claim 1 wherein the preparation contains 360 mg of diltiazem.

44. The preparation of claim 1 wherein the preparation contains 420 mg of diltiazem.

45. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 39, 40, 41, 42, 43 or 44 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

46. The preparation of claim 15 wherein the wetting agent is selected from:

sugars;  
saccharose, mannitol, sorbitol;  
lecithins;  
C<sub>12</sub> to C<sub>20</sub> fatty acid esters of saccharose;  
xylose esters or xylites;  
polyoxyethylenic glycerides;  
esters of fatty acids and polyoxyethylene;  
sorbitan fatty acid ester;  
polyglycides-glycerides and polyglycides-alcohols ester;  
and metal salts.

47. The preparation of claim 10 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer selected from the group consisting of hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which enables the bead to be hydrated by the introduction of gastrointestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

48. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

49. A method of treatment of a patient's hypertension and/or angina comprising the administration of the prepa-

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ration of diltiazem of claim 47 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

50. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1 which comprises the following constituents:

	% W/W
(i) in the core:	
(a) Diltiazem hydrochloride	69-73
(b) Microcrystalline cellulose	8-9.5
(c) (Polyvinyl Pyrrolidone)	1-2
(d) Sucrose stearate	7-8
(ii) in the membrane:	
(e) Magnesium stearate NF	0.5-2.5
(f) Talc USP	0.5-5.0
(g) Titanium dioxide, (USP)	0.15-0.3
(h) Hydroxypropylmethylcellulose 2910	0.3-0.6
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01-0.025
(j) Simethicone C emulsion USP (dry of 30%)	0.01-0.015
(k) a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7-11
Purified water USP	0 (used for mixing).

51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 50 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

52. The preparation of claim 10 in which the core and membrane comprise:

- (i) in the core,
- (a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
- (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);
- together with suitable adjuvants; and
- (ii) in the membrane,
- (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;
- (d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethyl-cellulose, hydroxypropylcellulose, and any combination thereof; and
- (e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. The preparation of claim 10 in which the core and membrane comprise:

- (i) in the core,
- (a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

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(b) between about 7% and about 8% wetting agent (% w/w of the total preparation); together with suitable adjuvants; and  
(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

56. The preparation of claim 10 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

58. The controlled-release preparation of claim 2 in which the diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation); together with suitable adjuvants; and

(ii) in the membrane,

(c) between 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

59. The preparation of claim 58 wherein the microgranules are in capsule form.

60. The preparation of claim 58 wherein the microgranules are in tablet form.

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61. The preparation of claim 58 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation); together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

62. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1, which preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

	% w/w
(i) in the core:	
(a) Diltiazem hydrochloride	69-73
(b) Microcrystalline cellulose	8-9.5
(c) (Polyvinyl Pyrrolidone)	1-2
(d) Sucrose stearate	7-8
(ii) in the membrane:	
(e) Magnesium stearate NF	0.5-2.5
(f) Talc USP	0.5-5.0
(g) Titanium dioxide (USP)	0.15-0.3
(h) Hydroxypropylmethylcellulose 2910	0.3-0.6
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01-0.025
(j) Simethicone C emulsion USP. (dry of 30%)	0.01-0.015
(k) a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7-11
Purified water USP	0 (used for mixing).

63. The preparation of claim 58 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

64. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

65. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form

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of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;  
saccharose, mannitol, sorbitol;  
lecithins;  
C<sub>12</sub> to C<sub>20</sub> fatty acid esters of saccharose;  
xylose esters or xylites;  
polyoxyethylenic glycerides;  
esters of fatty acids and polyoxyethylene;  
sorbitan fatty acid esters;  
polyglycides-glycerides and polyglycides-alcohols ester,  
and metal salts.

66. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 65 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

67. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 63 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

68. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1

wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

	% W/W
(i) in the core:	
(a) Diltiazem hydrochloride	69-73
(b) Microcrystalline cellulose	8-9.5
(c) (Polyvinyl Pyrrolidone)	1-2
(d) Sucrose stearate	7-8
(ii) in the membrane:	
(e) Magnesium stearate NF	0.5-2.5
(f) Talc USP	0.5-5.0
(g) Titanium dioxide, (USP)	0.15-0.3
(h) Hydroxypropylmethylcellulose 2910	0.3-0.6
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01-0.025
(j) Simethicone C emulsion USP, (dry of 30%)	0.01-0.015
(k) neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7-11
Purified water USP	0 (used for mixing).

69. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 66 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

70. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 3, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

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(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);  
together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

71. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

72. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 3, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);  
together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

73. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

74. A controlled-release preparation of pharmaceutically acceptable form of diltiazem according to claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the

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central core comprises diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

- (i) in the core,
  - (a) between about 50% and about 85% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
  - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);
- together with suitable adjuvants; and
- (ii) in the membrane,
  - (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;
  - (d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and
  - (e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

75. The preparation of claim 74 wherein the microgranules are in capsule form.

76. The preparation of claim 74 wherein the microgranules are in tablet form.

77. The preparation of claim 74, 75 or 76 wherein the core and membrane comprise:

- (i) in the core,
  - (a) between about 69% and about 73% (% w/w of the total preparation) of diltiazem or pharmaceutically acceptable salt thereof; and
  - (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);
- together with suitable adjuvants; and
- (ii) in the membrane,
  - (c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, and magnesium stearate;
  - (d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and any combination thereof; and
  - (e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

78. The preparation of claim 74, 75 or 76 wherein the core and membrane comprise:

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	% W/W
<u>(i) in the core:</u>	
(a) Diltiazem hydrochloride	69-73
(b) Microcrystalline cellulose	8-9.5
(c) (Polyvinyl Pyrrolidone)	1-2
(d) Sucrose stearate	7-8
<u>(ii) in the membrane:</u>	
(e) Magnesium stearate NF	0.5-2.5
(f) Talc USP	0.5-5.0
(g) Titanium dioxide (USP)	0.15-0.3
(h) Hydroxypropylmethylcellulose 2910	0.3-0.6
(i) (Polyoxyethylene Sorbitan Monocoleate)	0.01-0.025
(j) Simethicone C emulsion USP (dry of 30%)	0.01-0.015
(k) a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7-11
Purified water USP	0 (used for mixing).

79. The preparation of claim 74 or 76 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of diltiazem during the tablet process, together with suitable excipients and adjuvants.

80. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 74, 75 or 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

81. The controlled release preparation of claim 1 wherein said neutral acrylic polymer is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester.

82. The preparation of claim 70, 72 and 74 wherein the lubricant is selected from the group consisting of talc, and magnesium stearate.

83. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

84. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of diltiazem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

85. The preparation of claim 1 in capsule form.

86. The preparation of claim 1 in tablet form.

87. The preparation of claim 2 in capsule form.

88. The preparation of claim 2 in tablet form.

\* \* \* \* \*

**TAB C**

**THIS EXHIBIT HAS BEEN  
REDACTED IN ITS ENTIRETY**



**CERTIFICATE OF SERVICE**

I, the undersigned, hereby certify that on May 2, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Richard L. Horwitz  
POTTER ANDERSON & CORROON LLP

and that I caused copies to be served upon the following in the manner indicated:

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*/s/ Karen Jacobs Loudon*

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